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(57) Abstract

ECG signals are received from the patient (102), processed (103) to determine deviations from the normal and displayed (104) either as a frequency transformed signal or as a graph of the signal against one of its derivatives in a phase plane plot. The results, depending on the signal and circumstances may be interpreted to obtain information about heart disorders, the degree of drug toxicity or the efficacy of a particular drug. Further, an automatic defibrillator uses the ECG signal received (703) from the patient and processes (704) processing to determine the amount of energy to be discharged into the heart by the shock device (705).

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DESCRIPTION

Methods for Detecting and Evaluating Heart Disorders

Cross-Reference to Related Application

This application is a continuation-in-part of copending application S.N. 541,881, filed June 20, 1990 in the name of the same inventors and with the same title.

Background of the Invention

1. Field of the Invention

This invention relates to heart disorders. More specifically, this invention relates to detecting and evaluating arrythmia, fibrillation and related disorders by manipulation of an electrocardiogram signal.

2. Description of Related Art

Despite major advances in the diagnosis and treatment of ischemic heart disease over the past decade, a substantial number of patients each year may suffer sudden cardiac death as a consequence of ventricular fibrillation (VF). To date, no reliable predictive or preventive measures have been developed. By all outward appearances, VF is a highly complex, seemingly random phenomenon. So are other related heart disorders, including those stages in heart behavior which typically precede VF (onset of VF). Accordingly, it is difficult for automated devices to determine with any reliability that a patient is undergoing VF or onset of VF. Moreover, onset of VF may also be difficult to determine with any reliability, even for skilled medical personnel.

A method of detecting and evaluating heart disorders would therefore find wide applicability and utility. Patient monitoring devices may summon medical personnel if the patient is undergoing VF or onset of VF. Automatic

devices which attempt to counter VF, e.g. automatic implantable cardiac defibrillators (AICDs) may vary their operation based on evaluation of the severity of the patient's condition. Methods for reliably evaluating the risk of VF may also have important utility in monitoring patients undergoing surgery or other critical therapy.

It has been found that some anti-arrhythmic drugs may also have a pro-arrhythmic effect in excess concentrations. For example, quinidine has been known to be toxic in this manner. A method of detecting and evaluating heart disorders would also have wide applicability and utility in determining if a patient has been subjected to a toxic (or partially toxic) dosage of a drug relating to heart condition.

Chaos theory is a recently developed field relating to phenomena which appear to be highly complex and seemingly random, but which may be described as the deterministic result of relatively simple systems. Chaos theory may have potentially wide applications in biologic and other systems involving ambiguity and uncertainty. For example, it has been conjectured that chaos theory may be valuable for describing certain natural processes, including electroencephalogram (EEG) and electrocardiogram (EKG) signals. Techniques for detecting and evaluating aspects of deterministic chaos are known in the field of chaos theory, but have found little application in the medical field.

Accordingly, there is a need for improved methods and devices for detecting and evaluating heart disorders, including ventricular fibrillation (VF) and the onset of VF.

Summary of the Invention

A first aspect of the invention provides a method for detecting a heart disorder, by examination of a phase-plane plot (PPP) of a patient electrocardiogram (EKG). A normal patient will have a PPP which is relatively smooth;

a patient at risk of developing ventricular fibrillation (VF) onset will have a PPP which exhibits features of a chaotic process, such as multiple bands, "forbidden zones", periodicity with period-doubling and phase locking; a patient exhibiting VF will have a PPP which appears noisy and irregular. Differing PPPs may be readily recognized, thus detecting patients with heart disorders.

In a preferred embodiment, the PPP's degree of deterministic chaos may be measured by a processor, such as by graphic and numeric analysis. (1) The processor may measure a Lyapunov exponent or a fractal dimension of the PPP. (2) The processor may determine a Poincare section of the PPP and examine that Poincare section for indicators of deterministic chaos. Also, the processed PPP and Poincare sections may be reviewed by a human operator.

A second aspect of the invention provides a method for detecting a heart disorder, by examination of a frequency-domain transform (such as an FFT) of a patient EKG. A normal patient will have an FFT with a discrete spectrum, while a patient exhibiting VF will have an FFT with a relatively continuous spectrum and a peak energy at a relatively low frequency (e.g., about 5-6 Hz). A patient exhibiting VF which is difficult to revert with shock will have an FFT with a peak energy at a relatively high frequency (e.g., about 10 Hz or more).

In a preferred embodiment, an automatic defibrillating device may comprise means for delivering a variable shock, the size of which is determined at least in part by the FFT's peak energy. The defibrillating device may also comprise means for signalling an alarm if the FFT's peak energy is at a relatively high frequency.

A third aspect of the invention provides a method for detecting drug toxicity, based on particulars of an action-potential duration (APD) restitution curve, or an action-potential amplitude (APA) curve, which is con-

structed for the patient, such as fitting an exponential relation to that curve or such as a parameter time constant for that curve. The slope of the fitted curve will indicate the patient's possibility of predisposition to arrythmia. Differences in the parameters of the fitted curve allow one to distinguish between normal and abnormal patients, e.g. those at risk of arrythmia or ischemia. A normal patient will have a relatively low parameter time constant; a patient who is exhibiting drug toxicity will have a relatively high parameter time constant. A PPP of APD or APA data may also be generated, and the analytical techniques described herein may be utilized to interpret that PPP, to determine and evaluate drug toxicity.

Brief Description of the Drawings

Figure 1 shows a patient monitoring system.

Figure 2 shows a set of sample EKG signals.

Figure 3 shows a set of corresponding PPPs for the sample EKG signals of figure 2.

Figure 4 shows an example PPP and a corresponding Poincare section.

Figure 5 shows an example PPP and a corresponding time-lapse Poincare section.

Figure 6 shows a set of corresponding frequency-domain transforms, obtained by performing a fast Fourier transform (FFT) on the EKG signal.

Figure 7 shows an improved automatic implantable cardiac defibrillator ("AICD").

Figure 8 shows a signal response of an individual heart muscle cell to a stimulus, known in the art as "action potential".

Description of the Preferred Embodiment

A first aspect of the invention relates to detection and evaluation of heart disorders by examination of a phase-plane plot (PPP) of a patient electrocardiogram (EKG).

Figure 1 shows a patient monitoring system. A patient 101 is coupled to an electrocardiogram (EKG) device 102, which acquires EKG signals and transmits them to a processor 103. The processor 103 may display the EKG signals on a monitor 104 (as is well-known in the art), or it may process the EKG signals and display any results of processing on the monitor 104.

EKG signals are well-known in the art, as are methods of acquiring them. As used herein, an EKG refers to a surface electrocardiogram, but other forms of electrocardiogram would also work with the methods disclosed herein, and are within the scope and spirit of the invention. For example, the EKG shown herein may comprise a surface EKG, an epicardial EKG, an endocardial EKG, or another related signal (or set of signals) measured in or near the heart. Moreover, the signal which is manipulated may be a voltage signal, a current signal, or another related electromagnetic values (or set of values).

Figure 2 shows a set of sample EKG signals. A first EKG signal 201 shows a normal patient. A second EKG signal 202 shows a patient in transition to VF. A third EKG signal 203 shows a patient with VF.

The processor 103 may construct a phase-plane plot (PPP) from the EKG signal. A first type of PPP comprises a plot of an EKG variable against its first derivative. In a preferred embodiment, the EKG variable is voltage, v (itself a function of time); its first derivative is dv/dt (also a function of time).

However, it would be clear to one of ordinary skill in the art, after perusal of the specification, drawings and claims herein, that wide latitude in construction of the PPP is possible. The variable chosen for the PPP may be any one of a variety of different parameters, including EKG voltage, current, or another signal value. The chosen variable (v) may be plotted against its first time derivative (dv/dt), its second time derivative d^2v/dt^2, or

another time derivative $d^n v/dt^n$. Or, an Mth derivative may be plotted against an Nth derivative.

Another type of PPP may comprise a plot of an EKG variable (or an Nth derivative thereof) against a time delayed version of itself, (e.g. v(t) versus $v(t-\delta t)$). This type of PPP is sometimes also called a "return map". This type of PPP is less sensitive to EKG signal noise.

Another type of PPP may comprise a plot of three EKG variables (or Nth derivatives thereof) simultaneously (e.g., v, dv/dt, and d^2v/dt^2). Such a PPP would be 3-dimensional. Where the PPP is 3-dimensional, it may be displayed stereoscopically, or a 2-dimensional plane "cut" of the 3-dimensional display may be displayed on a 2-dimensional display. It would be clear to one of ordinary skill in the art, that all of these choices described herein, or combinations thereof, would be workable, and are within the scope and spirit of the invention.

Figure 3 shows a set of corresponding PPPs for the sample EKG signals of figure 2. A first PPP 301 corresponds to the first EKG signal 201. A second PPP 302 corresponds to the second EKG signal 202. A third PPP 303 corresponds to the third EKG signal 203.

Part of this aspect of the invention is the discovery that a normal patient will have a PPP which exhibits the regularity and smoothness of an EKG signal from that normal patient, while a patient undergoing VF will have a PPP which exhibits the irregularity and complexity of an EKG signal which might be deterministic chaos (e.g., a periodicity, banding and "forbidden zones"). Moreover, a patient in transition from normal into VF (i.e., in VF onset) exhibits a PPP which is consistent with an assessment that the EKG signal for the patient is in transition to deterministic chaos.

A normal patient has a relatively regular beat-to-beat EKG signal. As the patient transitions to VF, the patient's EKG signal at first shows oscillations between pairs of alterant regular beat-to-beat signals. As the

transition continues, the patient's EKG signal then shows oscillations between greater and greater numbers of alterant regular signals (e.g., four possible alternants, eight possible alternants, etc.), until it is no longer possible to identify alterant regular signals and the EKG signal is irregular and highly complex. At that point, the patient is generally said to be exhibiting VF.

In like manner, the patient's PPP will transition from a smooth single-banded display, through a multi-banded display (showing multiple alternants) and finally to an irregular and highly complex display. The display change in the PPP is so striking that even a relatively untrained person can see the difference. This is in contrast with display changes in the EKG, which generally requires a skilled cardiologist to evaluate.

There are several possible factors which might cause a patient to transition from normal to VF. These factors may include drug overdose (especially overdose with an anti-arrhythmic which has a pro-arrhythmic effect in overdosage, e.g., quinidine intoxication), excessive electrical stimulation, hypothermia, ischemia, and stress. In a preferred embodiment, a patient monitor may examine the patient's PPP so as to determine if the patient is in transition from normal to VF; this could indicate that one of these pro-arrhythmic factors is excessively present.

The processor 103 may further process the PPP so as to measure the PPP's degree of deterministic chaos. Several techniques may be applied for this purpose:

(1) The processor 103 may measure a Lyapunov exponent of the PPP. The Lyapunov exponent of the PPP is a measure of the degree to which nearby paths of the PPP diverge. The Lyapunov exponent is well-known in chaos theory and may be measured with available software. See, e.g., Wolf et al., "Determining Lyapunov exponents from a time series", Physica D 1985;16:285-317.

(2) The processor 103 may measure a fractal dimension of the PPP. The fractal dimension of the PPP is a measure of the degree to which the PPP forms a "space-filling" curve. The fractal dimension is well-known in chaos theory and may be measured with several techniques (e.g. correlation dimension or box-counting methods), for example as shown below:

To measure the fractal dimension of the PPP, the processor 103 superimposes a rectilinear grid (comprising a set of boxes) on the PPP and counts the number of boxes which are cut by the PPP's trace. The processor 103 varies the size of the grid and records each grid size and each count. The processor 103 then computes the constant k in the following relation:

$$\ln(\#\text{ of boxes cut}) = k * \ln(\#\text{ of boxes in grid}) \quad (4)$$

The constant k is a measure of the fractal dimension of the PPP. A value of k between about 3 and about 7, especially with a fractional component, implies that the PPP is likely to represent a process based on deterministic chaos, and therefore a patient who is close to (or actually in) VF.

(3) The processor 103 may determine a Poincare section of the PPP and examine that Poincare section for indicators of deterministic chaos, as described herein. The processed PPP and Poincare sections may also be displayed for review by a human operator, whereupon any visible structure will be readily recognized.

Figure 4 shows an example PPP 401 and a corresponding Poincare section 402. A Poincare section may comprise a line segment drawn across a part of the PPP. In general, such a line segment will be close to perpendicular to the trajectories of the PPP in a region of interest.

The processor 103 may acquire the data points in each Poincare section or PPP and compute a statistical measure of anisotropy or inhomogeneity of those data points. One such measure is based on the mean and standard deviation

of those data points (these may be computed by statistical methods which are well-known in the art). The ratio

r = (standard deviation) / (expected value) (403)

is a measure of the degree of clumping in the Poincare section.

A greater value for r implies that the PPP is more likely to represent a process based on deterministic chaos, and therefore a patient who is close to (or actually in) VF. The value for r may be displayed for review by a human operator in comparison with a value for r for a normal patient, together with a set of confidence bands, as is well-known in the art, for indicating a degree of variation from a normal patient.

The processor 103 may also compute other statistical measures of the Poincare section.

The processor 103 may also determine a "time-lapse" Poincare section of the PPP.

Figure 5 shows an example PPP 501 and a corresponding time-lapse Poincare section 502. A time-lapse Poincare section may comprise a set of data points selected from the PPP by selecting one data point every t seconds. The time-lapse Poincare section may be analyzed in like manner as the other Poincare section disclosed herein.

A second aspect of the invention relates to detection and evaluation of heart disorders based on a frequency-domain transform of a patient EKG.

Figure 6 shows a set of corresponding frequency-domain transforms, obtained by performing an FFT on the EKG signal. A first transform 601 corresponds to a first EKG signal (not shown). A second transform 602 corresponds to a second EKG signal (not shown).

In the first transform 601, representing a normal patient, the frequency spectrum shows that the energy of the corresponding EKG signal occurs primarily at a discrete set of frequencies. In the second transform 602, representing a patient exhibiting VF, the frequency spectrum shows that the energy of the corresponding EKG

signal has a continuous spectrum of frequencies, and has an energy peak 603.

Part of this aspect of the invention is the use of both visual and mathematical techniques for analyzing frequency domain transforms, including for example calculation of a harmonic magnitude ratio (HMR). To determine the HMR, a major peak or a central region of energy distribution in a spectrum of a frequency domain transform (such as an FFT) may be identified, and the HMR calculated as follows: A magnitude of the transform in the region of the identified point is determined (e.g., by summing the magnitude of the transform at the identified point and at surrounding points), and is summed with the corresponding magnitude in the region of harmonic values of the frequency for the identified point. This sum is divided by a total magnitude of the transform for the entire signal; the ratio is defined as the HMR.

One method which is known for bringing a patient out of VF ("defibrillating") is to administer an electric shock across the patient's heart. This electric shock must generally have a substantial energy, e.g. 10-20 joules, and may often cause tissue damage to the patient even if it is successful in defibrillating the patient. Multiple shocks may be required, generally of increasing energy. Accordingly, it would be advantageous to use a larger shock only when necessary, and it would be advantageous to use as few shocks as possible.

Part of this aspect of the invention is the discovery that when the energy peak 603 of the frequency-domain transform 602 is at a relatively low frequency, a relatively low energy shock will generally suffice to defibrillate the patient. When the energy peak 603 of the frequency-domain transform 602 is at a relatively high frequency (also, when a secondary energy peak 604 appears in the frequency-domain transform 602 at a relatively high frequency), it will require a relatively high energy shock to defibrillate the patient, if it is possible to

defibrillate the patient by means of an electric shock at all.

One application of this discovery is in automated implanted cardiac defibrillators (AICDs), which attempt to automatically detect VF and to automatically administer a shock to defibrillate the patient.

Figure 7 shows an improved AICD 701. A patient 702 is coupled to an AICD EKG 703, which acquires EKG signals and transmits them to an AICD processor 704, which controls a shock device 705 for administering a defibrillating shock to the patient 702.

The improved AICD 701 also comprises (e.g., as part of the AICD processor 704) software for determining an FFT of the EKG signal and for determining the energy peak in that FFT. If the energy peak in that FFT is relatively low, the AICD processor 704 controls the shock device 705 to administer a relatively small shock to the patient. If the energy peak in that FFT is relatively high, the AICD processor 704 controls the shock device 705 to administer a relatively large shock to the patient, and may also signal an alarm 706 or other indicator that defibrillation may not be successful.

A third aspect of the invention relates to detection and evaluation of drug toxicity based on a parameter time constant for an action-potential duration (APD) restitution curve or an action-potential amplitude (APA) curve which is constructed for the patient.

Figure 8 shows a signal response of an individual heart muscle cell to a stimulus. This individual cell response is known in the art as "action potential".

It is well-known in the art that a time duration for recovery 801 of an individual cell depends on factors including a resting period 802 which the cell has had prior to stimulus. It is also well-known in the art that an APD restitution curve can be constructed for a human patient with the use of an intracardiac catheter. However, the complete relation between the actual time

duration for recovery 801 based on the resting period 802 is not known.

Part of this aspect of the invention is the discovery that when the time duration for recovery 801 is plotted against the resting period 802 (diastolic interval), the curve follows an exponential relation:

$$APD = APD_{pl} - A * \exp(-DI/tau) \quad (803)$$

where APD_{pl} is the plateau APD, A is a proportionality constant, DI is the diastolic interval, and tau is the parameter time constant

The nonlinear nature of the APD restitution curve may promote deterministic chaos in response to excessive stimulus of the heart muscle cells. When the APD restitution curve is steeper (i.e., the parameter time constant tau is larger), there is accordingly a greater predilection for the heart to enter VF. Thus, another part of this aspect of the invention is the discovery that a normal patient will have a relatively low APD restitution parameter time constant, while a patient who is exhibiting drug toxicity (e.g., quinidine intoxication) will have a relatively high APD restitution parameter time constant. The restitution parameter time constant may also be used in monitoring cardiac stability, and in evaluating efficacy of anti-arrhythmic drugs.

Experimental verification of the present invention has been achieved by the inventors.

Experiment I.

A mathematical study used PPPs, return maps, Poincare sections, correlation dimension, and spectral analysis to distinguish periodic, chaotic and random signals. PPPs were useful in distinguishing among all three classes of signals. Periodic signals showed clear, widely separated trajectories; chaotic signals showed banding, forbidden zones and sensitive dependence on initial conditions; random signals showed no clear internal structure. With the exception of noise effects, the only major difference

between the PPPs and the appropriately lagged return map was a 45 degree rotation. Poincare sections were also able to distinguish among the three classes of signals: periodic signals showed isolated points; chaotic signals showed ordered areas of apparent self-similarity; random signals showed a Gaussian distribution of points. Correlation dimension was more able to distinguish between chaotic and random signals than between chaotic and periodic signals. Spectral analysis using FFTs and harmonic magnitude ratio (HMR) was able to distinguish periodic signals, but were unable to distinguish between random and chaotic signals: HMRs of periodic signals were greater than 97%; HMRs of chaotic signals varied between 17 and 80%; HMRs of random signals were approximately 40%. PPPs were greatly affected by noise, return maps were less affected, while spectral analysis was relatively immune to noise. It was concluded that PPPs, return maps, Poincare sections, correlation dimension and spectral analysis are all useful determinatives of chaotic systems.

Experiment II.

A mathematical study concentrated specifically on ability of spectral analysis to distinguish chaotic from random signals. In this experiment, two series of random signals were generated. The first series comprised 5000 pseudo-random numbers which were smoothed using a method of least-squares approximation. The second series comprised white noise obtained from an analog-to-digital conversion board. Spectral analysis was performed by applying an FFT to the data, and searching for a broad band spectrum or a change from a narrow band to a broad band, which was presumed to be diagnostic of chaos. It was concluded that spectral analysis by itself was insufficient to unequivocally distinguish chaotic signals from random signals, and that additional tests such as PPPs and return maps were necessary for this purpose.

Experiment III.

An experiment examined spectral analysis, visualization of PPPs and correlation dimension analysis, for usefulness in distinguishing between normal sinus rhythm and VF in dogs. Ischemia and re-perfusion were used as stress factors in closed-chest anesthetized dogs. Spectral analysis of the dogs having normal sinus rhythm revealed narrow-band spectra with fundamental frequencies at the sinus rate and harmonics extending beyond 50 Hz. PPPs were consistent with periodic dynamics, and dimension analysis revealed low dimensional behavior (1--2.5). In contrast, spectral analysis of the dogs having VF, revealed broad-band behavior with most of the energy at 6 Hz, and with energy at all frequencies between 1 and 25 Hz. PPPs showed constrained aperiodic behavior, and the dimensional analysis revealed higher dimensions (4-6) than that observed for the normal sinus rhythm dogs. Thus, all three techniques proved useful in distinguishing normal sinus rhythm from VF.

Experiment IV.

An experiment examined spectral analysis, visualization of PPPs, visualization of return maps, and correlation dimension analysis, for their usefulness in identifying VF in humans. These analytical techniques were applied to data from eight hypothermic patients undergoing spontaneous VF, and also to data from three normothermic patients with VF induced during electrophysiology testing. All patients had a broad band frequency spectrum (0-12 Hz), a low dimension (range 2-5), and banding and forbidden zones on PPPs and return maps. It was concluded that spectral analysis, visualization of PPPs, visualization of return maps, and correlation dimension analysis are useful in detecting and evaluating VF.

Experiment V.

An experiment examined spectral analysis, visualization of PPPs and correlation dimension analysis for their usefulness in distinguishing between normal sinus rhythm and VF in humans. VF in eight hypothermic human patients undergoing open-heart surgery was studied. In all patients, first and second order PPPs showed forbidden zones and banding, and an FFT revealed a relatively continuous power spectrum at all frequencies from zero to 25 Hz, with a majority of the power below 12 Hz. In contrast, correlation dimension in all cases was less than 4. It was concluded that multiphasic analysis of the data is preferable to reliance on a single analytical technique such as correlation dimension.

Experiment VI.

An experiment utilized spectral analysis and visualization of PPPs to elucidate the heterogenous nature of atrial fibrillation. In the experiment, the researchers induced acute fibrillation by a rapid train of stimuli to the atria of seven closed-chested dogs. PPPs based on the EKG data often inscribed well defined structures, and an FFT of the digitized EKGs showed peaks mostly below 15 Hz that were either discrete with clear harmonic components, or had continuous spectra that changed in a time- and site-dependent manner. It was concluded that both spectral analysis and visualization of PPPs are useful techniques for analyzing atrial as well as ventricular fibrillation.

Experiment VII.

In an experiment, visual analysis of PPPs and the slope of an APD restitution curve were found to be useful for detecting and evaluating quinidine-induced VF in in vivo hearts. Quinidine was administered at 30 minute intervals over five hours, until either a total of 90-100 mg/kg was administered or until ventricular tachycardia or

VF occurred, whichever came first. PPPs of the quinidine intoxicated cells demonstrated sensitive dependence on initial conditions and the presence of forbidden zones, and the corresponding FFTs showed continuous spectra. In contrast, PPPs of cells in a control dog were uniform and densely packed, and the corresponding FFTs showed discrete spectra. The initial slope of the APD restitution curve of quinidine intoxicated cells was much steeper, by at least an order of magnitude, than the slope of normal cells. It was concluded that quinidine toxicity correlates with the slope of the APD restitution curves.

Experiment VIII.

An experiment compared the slope of the APD and APA restitution curves with quinidine intoxication. Quinidine was administered (90-100 mg/kg) to eight dogs over a five hour period. Three untreated dogs served as controls. Ventricular and Purkinje cells from both treated and untreated dogs were then subjected to electrical stimulation with cycles from 900 to below 600 msec. Shortening of the cycle length to 600 msec resulted in irregular dynamics of both APD and APA, including electrical alternans and bifurcation. The slope of an APD restitution curve was calculated, and found to be steeper in quinidine-intoxicated cells for both Purkinje fibers and ventricular muscle cells than the slope during quinidine washout or in normal untreated cells. The curve could be fit by the exponential equation given herein. APA changes were almost always correlated with the APD changes. In the three normal tissue preparations neither ventricular muscle cells nor Purkinje cells showed bifurcative behavior with respect to APD or AA. It was concluded that quinidine toxicity, and presumably other drug-induced pro-arrhythmic effects, correlate with the slope of both APD and APA restitution curves.

Experiment IX.

In an experiment, quinidine-induced ventricular tachycardia and VF in dogs was analyzed using PPPs generated from action potential duration (APD) and action potential amplitude (APA) data. Both PPPs showed forbidden zones and sensitive dependence on initial conditions which are indicative of chaos. It was concluded that PPPs based on either APD or APA are useful in detecting and evaluating quinidine toxicity.

Experiment X.

In an experiment, EKGs of quinidine intoxicated dogs were analyzed by frequency spectra, phase plane plots, Poincare sections, return maps and Lyapunov exponents. In the control state and at therapeutic doses, PPPs were uniformly thick and showed no gaps, indicating that cycle-to-cycle variation was due to normal biological "noise". But as the quinidine dose was increased to intermediate levels (40-50 mg/kg), PPPs showed clear non-uniform thickening, indicating sensitive dependence on initial conditions, and also showed marked banding (densely filled regions separated by divisions or gaps). At these intermediate doses, Lyapunov exponents became positive and Poincare return maps also indicated nonrandom chaos. At still higher doses, PPPs became more complex. In two dogs that did exhibit VF (and not in another) there was a significant change in the PPP at the last pre-fibrillatory dose: the development of a "funnel", a classic mechanism of chaos. Frequency spectra at all pre-fibrillatory doses were discrete, with peaks at a fundamental frequency and multiple harmonics. It was concluded that chaos does occur during progressive quinidine intoxication, and that PPPs, and graphic and numeric analysis based on the PPPs, are better indicators of chaos than frequency spectra.

Experiment XI.

In an experiment, quinidine toxicity in dogs was analyzed using PPPs generated from APA and APD data. EKG recordings were made at various driving rates from 1000 to 500 msec. Increase in the driving rate from 1000 to 500 msec caused the progressive appearance of higher order periodicities (period 3 and 4). Phase locking was seen with a stimulus (S) response (R) pattern repeating periodically in all 4 preparations at S:R ratios of 2:1, 5:3, 3:2. At faster drive rates aperiodic variations in APA and APD were observed. A number of intermediate stages that presage chaos were also seen in the quinidine intoxicated fibers. These results further demonstrate the usefulness of the methods of the present invention to detect both quinidine intoxication and precursor stages to intoxication.

Experiment XII.

In an experiment, quinidine toxicity in dogs was analyzed using PPPs generated from APA and APD data. Electrical stimuli were used to drive cardiac tissue at various rates from 2000 to under 300 msec. These stimuli caused steady alternans (bifurcation) in APD and APA of 108 ± 36 msec and 12 ± 9 millivolts respectively. Further increase in driving rates gave rise to irregular dynamics. This transition was preceded by various repeating stimulus-response ratios (phase-locking) for up to fifty consecutive beats. No such dynamics could be induced in three non treated (control) tissues. The APD restitution curve had significantly ($p < 0.05$) steeper slope than six control fibers. Stimulus-response latency remained constant at 6-9 msec. PPPs of the APDs during the irregular dynamics showed sensitive dependence on initial conditions and forbidden zones consistent with chaos theory. These results further demonstrate the usefulness of the methods of the present invention to detect both

quinidine intoxication and precursor stages to intoxication.

Experiment XIII.

An experiment used spectral analysis, PPPs, Poincare sections, Lyapunov Exponents and dimension analysis to analyze computer simulated waveforms including sine waves, modulated sine waves, square waves, saw toothed waves, and triangular waves. The researchers added random noise to the waveforms at 1%, 10% and 20%. The experiment further used the same analytical techniques on EKG data from anesthetized dogs in which VF was precipitated by five different interventions: quinidine intoxication; premature electrical stimulation followed by quinidine intoxication; coronary occlusion; reperfusion of acutely ischemic myocardium; and global hypothermia. The preliminary results showed that PPPs and Poincare sections in dogs undergoing ventricular fibrillation were consistent with chaos, while spectral analysis was not suggestive of chaos. The researchers concluded in part that VF can be described as chaotic electrophysiological behavior, but that single methods of analysis are not sufficient to detect such behavior.

One conclusion which may be drawn from the research cited herein is that the analytical value of each of the aspects of the invention may be enhanced through combination with one or more of the other aspects of the invention. A preferred embodiment of the present invention may include a combination of the aspects of the invention described herein. One preferred embodiment may comprise multiphasic analysis of a PPP (e.g., visually with a display, graphically with Poincare sections, and numerically with Lyapunov exponents and correlation dimension), frequency spectral analysis, and mathematical analysis of an APD restitution curve.

Alternative Embodiments

While preferred embodiments are disclosed herein, many variations are possible which remain within the concept and scope of the invention, and these variations would become clear to one of ordinary skill in the art after perusal of the specification, drawings and claims herein.

It would also become clear to one of ordinary skill in the art that embodiments of the invention may comprise means for continuous monitoring of drug toxicity, atrial fibrillation, ischemia or other heart conditions, such as during surgery or patient recovery from surgery. Moreover, embodiments of the invention may comprise means for indicating heart conditions which are detected to attending medical personnel or to the patient. In one preferred embodiment of the invention, means may be provided for directing the patient (when a heart disorder is detected) to contact a physician or to proceed to a nearby hospital for treatment.

Claims

1. A method for detecting heart disorders, comprising the steps of

receiving an electrocardiogram signal;

determining a phase-plane plot of said electrocardiogram signal; and

determining if said phase-plane plot indicates a heart disorder.

2. A method as in claim 1, wherein said heart disorders are one of the group: ischemia, electrical instability, drug toxicity.

3. A method as in claim 1, wherein said phase-plane plot comprises a multi-dimensional plot of at least two variables.

4. A method as in claim 1, wherein said phase-plane plot comprises a multi-dimensional plot of at least three variables.

5. A method as in claim 1, wherein said phase-plane plot comprises a plot of a signal voltage against a derivative of said signal voltage.

6. A method as in claim 5, wherein said derivative is a first derivative.

7. A method as in claim 1, wherein said step of determining if said phase-plane plot indicates a heart disorder comprises the step of determining a fractal dimension of said phase-plane plot.

8. A method as in claim 1, wherein said step of determining if said phase-plane plot indicates a heart disorder comprises the step of determining a Lyapunov exponent of said phase-plane plot.

9. A method as in claim 1, wherein said step of determining if said phase-plane plot indicates a heart disorder comprises the step of determining the presence of at least one of: banding, forbidden zones, nonuniform thickening, periodicity, aperiodicity.

10. A method as in claim 1, wherein said step of determining if said phase-plane plot indicates a heart disorder comprises the step of determining the presence of multiple alternants.

11. A method for detecting heart disorders, comprising the steps of

receiving an electrocardiogram signal;

determining a phase-plane plot of said electrocardiogram signal;

determining a Poincare section of said phase-plane plot; and

determining if said Poincare section indicates a heart disorder.

12. A method as in claim 11, wherein said phase-plane plot comprises a multi-dimensional plot of at least two variables.

13. A method as in claim 11, wherein said phase-plane plot comprises a multi-dimensional plot of at least three variables.

14. A method as in claim 11, wherein said phase-plane plot comprises a plot of a signal voltage against a derivative of said signal voltage.

15. A method as in claim 14, wherein said derivative is a first derivative.

16. A method as in claim 11, wherein said step of determining if said Poincare section indicates a heart disorder comprises the step of determining a statistical measure of at least one of: anisotropy, inhomogeneity.

17. A method for detecting heart disorders, comprising the steps of

receiving an electrocardiogram signal;

determining a frequency domain transform of said electrocardiogram signal;

determining if said frequency domain transform indicates a heart disorder.

18. A method as in claim 17, wherein said step of determining a frequency domain transform comprises the step of performing a Fourier transform.

19. A method as in claim 17, wherein said step of determining if said frequency domain transform indicates a heart disorder comprises the step of determining if said frequency domain transform comprises a continuous spectrum.

20. A method as in claim 17, wherein said step of determining if said frequency domain transform indicates a heart disorder comprises the step of determining if said frequency domain transform comprises an energy peak at a relatively high frequency.

21. A method as in claim 20, wherein said relatively high frequency is greater than about 6 Hz.

22. A method as in claim 20, wherein said relatively high frequency is greater than about 10 Hz.

23. An automated implantable cardiac defibrillator, comprising

means for receiving an electrocardiogram signal from a patient;

means for administering a defibrillating shock from said patient;

means for processing said electrocardiogram signal and for controlling said means for administering, wherein said means for processing causes said means for administering to administer a shock whose energy depends on a frequency domain transform of said electrocardiogram signal.

24. A defibrillator as in claim 23, wherein said energy is relatively greater when said frequency domain transform has an energy peak at a relatively greater frequency.

25. A method for detecting drug toxicity for a patient, comprising the steps of

constructing a relation between a diastolic interval and an action potential duration for said patient;

determining a value of a time constant for said relation; and

determining if said value indicates drug toxicity.

26. A method as in claim 25, wherein said step of determining if said value indicates drug toxicity comprises the step of determining if said value is substantially above a normal value.

27. A method for evaluating effectiveness of a drug for a patient, comprising the steps of

constructing a relation between a diastolic interval and an action potential duration for said patient;

determining a value of a time constant for said relation; and

determining if said value indicates that administration of said drug to said patient has an anti-arrhythmic effect.

28. A method for evaluating effectiveness of a drug for a patient, comprising the steps of

determining a set of action potential duration restitution data for said patient;

constructing a phase plane plot from said data; and

performing a multiphasic analysis of said phase plane plot to determine if said phase plane plot indicates that administration of said drug to said patient has an anti-arrhythmic effect.

29. A method as in claim 28, wherein said multiphasic analysis comprises at least one step of displaying said phase plane plot, computing a Poincare section of said phase plane plot, computing a Lyapunov exponent of said phase plane plot, or computing a correlation dimension of said phase plane plot.

30. A method for detecting heart disorders, comprising the steps of

receiving an electrocardiogram signal;

performing a plurality of the following steps to determining if said electrocardiogram signal indicates a heart disorder: (a) performing a multiphasic analysis of a phase-plane plot of said electrocardiogram signal, (b) performing a spectral analysis of said electrocardiogram signal, or (c) performing an analysis of an APD restitution curve computed in response to said electrocardiogram signal.

31. A method as in claim 30, wherein said step of performing a spectral analysis comprises the step of calculation of a harmonic magnitude ratio.

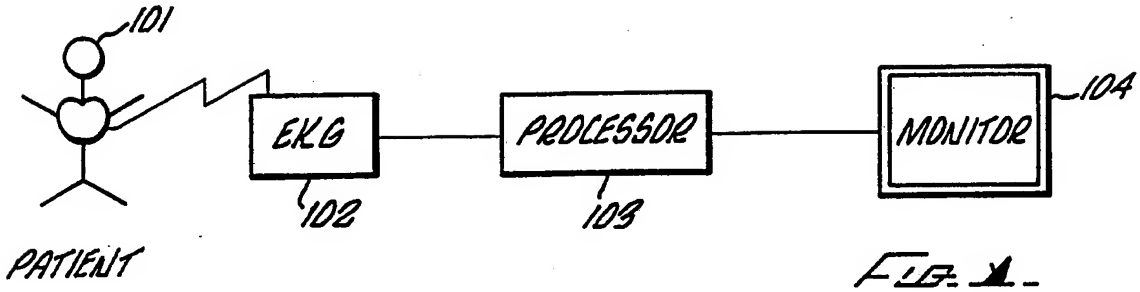


FIG. 1

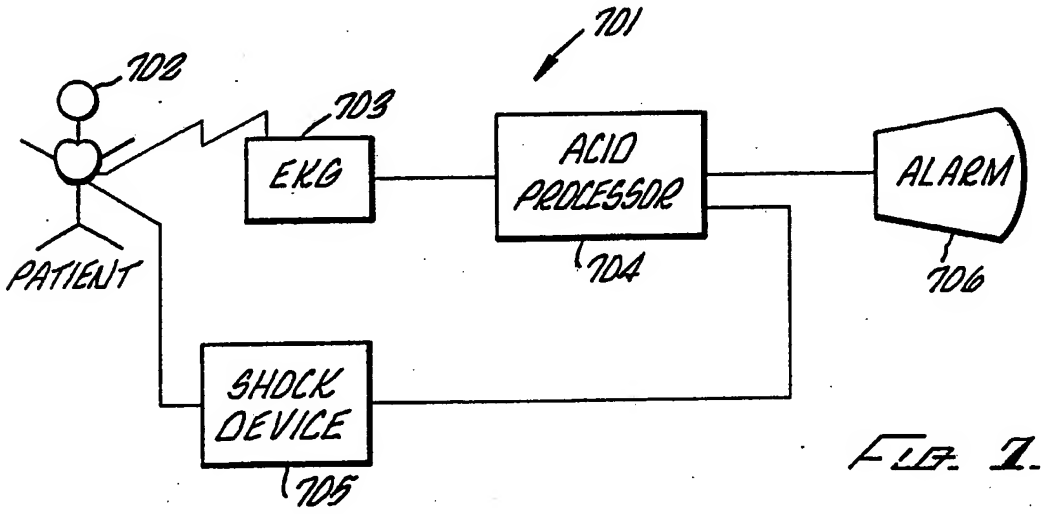


FIG. 7

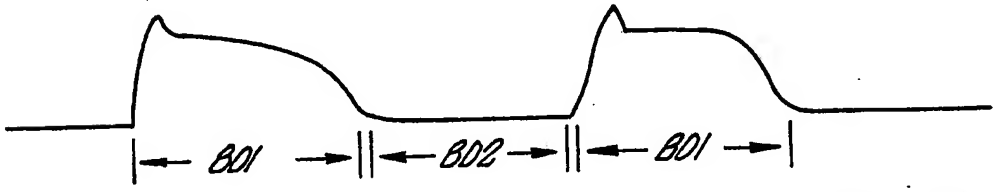


FIG. 8

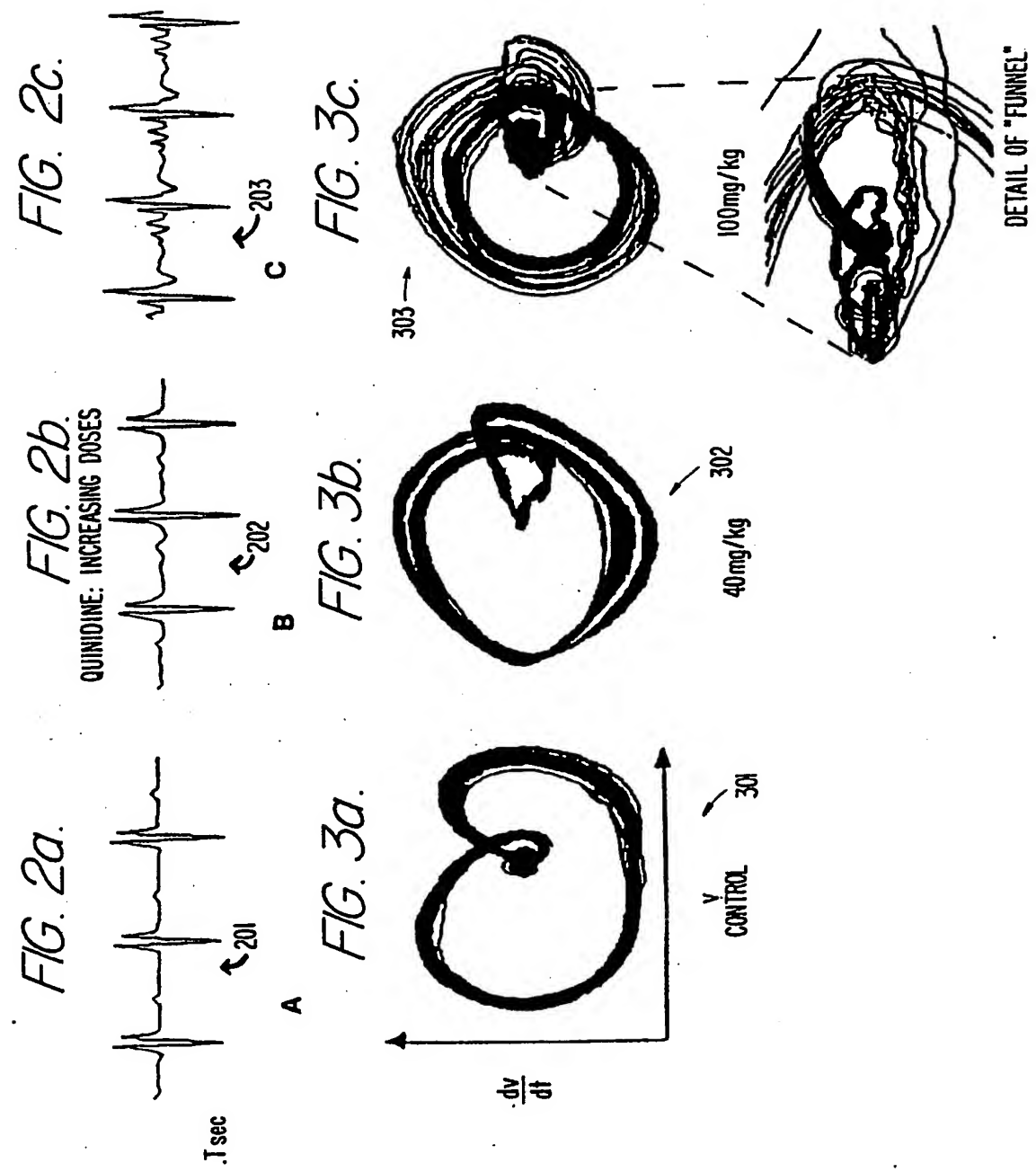
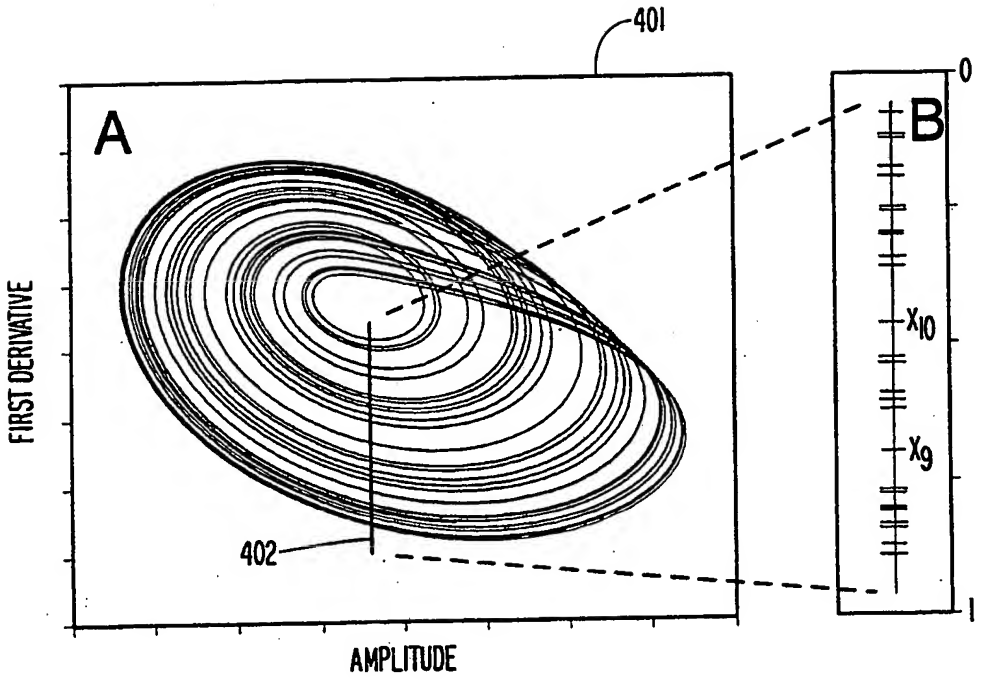


FIG. 2a.
201
A
1 sec
FIG. 2b.
QUINIDINE: INCREASING DOSES
202
B
FIG. 2c.
203
C
FIG. 3a.
301
V
CONTROL
dv/dt
FIG. 3b.
302
40mg/kg
FIG. 3c.
303
100mg/kg
DETAIL OF "FUNNEL"

FIG. 4.



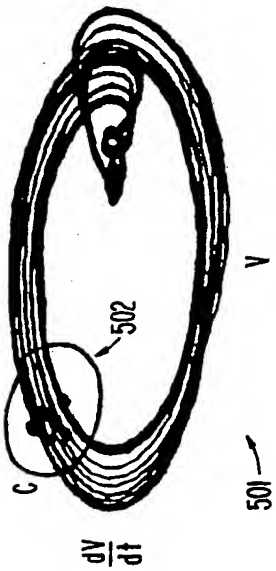


FIG. 5.

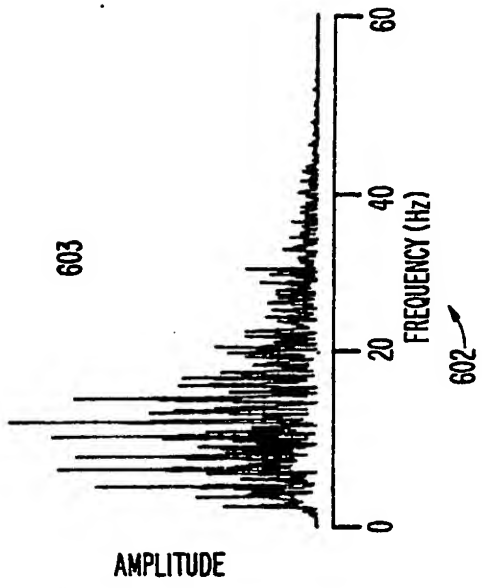


FIG. 6b.

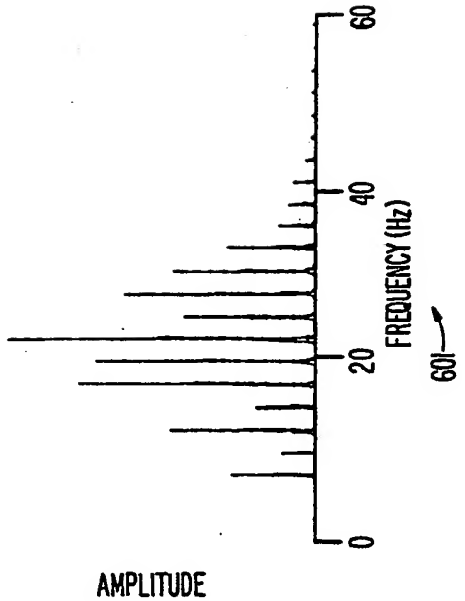


FIG. 6a

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/04000

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5) A61B 5/044
US CL. 128/712

II FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US	128/419D,696,699,700,702-704 364/413.05,413.06 424/2,9,10 424/2,9 514/259,596,821

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category [15]	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	US,A 3,929,125 BARNES et al 30 December 1975	1-16,30-31
A	US,A 3,940,692 NEILSON 24 FEbruary 1976	1-16,30-31
A	US,A 4,085,407 STRATBUCKER et al 18 April 1978	1-16,30-31
A	US,A 4,570,225 LUNDY 11 February 1986	1-16,30-31
A,E	US,A 4,979,110 ALBRECHT et al 18 December 1990	17-22
A	US,A 4,680,708 AMBOS et al 14 July 1987	17-22
X	US,A 4,924,875 CHAMOUN 15 May 1990 (See Abstract)	17-22
A,P	US,A 4,974,598 JOHN 04 December 1990 (See Fig. 3 and col. 8, lines 21-68)	17-22
Y	US,A 4,523,595 ZIBELL 18 June 1985 (Fig. 11d & col. 13, lines 20-68)	23-24
Y	US,A 4,403,614 ENGLE et al 13 September 1983 (See col. 8, lines 52-67)	23-24
A	US,A 4,384,585 ZIPES 24 May 1983	23-23

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [3]	Date of Mailing of this International Search Report [3]
11 August 1991	18 NOV 1991
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	William E. Kamm

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [1] not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [1], specifically:

3. ☐ Claim numbers_____, because they are decendent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

I. Claims 1-16, 30-31 drawn to a phase plane plot diagnostic method.
II. Claims 17-22 drawn to a frequency of main diagnostic method.
III. Claims 23-24 drawn to a defibrillator
IV. Claims 25-26 drawn to a drug toxicity test
V. Claims 27-29 drawn to a drug efficency test

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers . . searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international . . those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search . . the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Aut . . invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
A	US,A 4,673,563 BERNE et al 16 June 1987	25-29
A	US,A 4,377,592 AUROUSSEAU 22 March 1983	25-29

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

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(74) Agents: MURPHY, David, B. et al.; Lyon & Lyon, 611 West 6th Street, 34th Floor, Los Angeles, CA 90017 (US).

(81) Designated States: CA, FI, JP, NO, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: METHOD AND APPARATUS FOR CLOSED LOOP DRUG DELIVERY

(57) Abstract

A closed-loop drug delivery system uses patient response and rule based decision making methods to achieve operator specified responses for diagnostic purposes. In the preferred embodiment, cardiac diagnosis is performed by pharmacologically stressing the heart by administration of an exercise simulating agent drug. In the preferred method, a protocol is defined, which preferably includes a target for a physiologic variable, such as heart rate, and a plan to achieve that target value. Preferably, the plan includes a specification of the desired rate of increase in that variable, such as the rate of increase in the heart rate per minute. The plan comprises the desired changes in the physiologic variable as a function of time. While any desired function may be used, the more common modes include RAMP, HOLD, LEVEL and TARGET mode. In one aspect of this invention, the protocol may be varied by the operator after drug administration has begun. Futher, in one embodiment, the protocol includes a definition of an acceptable zone of deviation from the plan, such that if the patient physiologic variable deviates from the permissible zone, alternate control rules are implemented. Preferably, saturation detection and avoidance is implemented.

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DESCRIPTION

Method and Apparatus for Closed Loop Drug Delivery

Cross-Reference to Related Applications

This application is related to U.S. Serial No. 308,683, filed February 9, 1989, which is a continuation-in-part of U.S. Serial No. 157,875, filed February 19, 1988, the disclosures of which are incorporated herein by reference.

Field of the Invention

The invention relates generally to a closed loop drug delivery system using a rule based administration method. More particularly, the invention relates to methods and apparatus for use in the administration of an exercise simulating agent ("ESA") which elicits a cardiovascular response similar to that resulting from aerobic activity. This apparatus and method is used advantageously in the diagnosis, evaluation and treatment of coronary artery disease, by providing for closed loop drug delivery to generate a cardiac stress related response.

Background and Introduction to the Invention

Heart disease is the number one killer in the United States and a leading cause of death worldwide. Currently, heart disease, stroke and related disorders account for nearly one million deaths per year in the United States, almost as many deaths as from all other causes combined. Cardiovascular and cerebrovascular diseases affects approximately 65 million people in the United States, roughly one out of every four. Approximately 5 million people in the United States suffer from coronary artery disease ("CAD"), resulting in over 1.5 million heart attacks yearly, of which over 500,000 are fatal. The annual economic cost of cardiovascular disease alone is estimated to be 85 billion dollars.

Atherosclerosis is the most common form of arteriosclerosis, commonly referred to as 'hardening of the arteries'. Atherosclerosis is a degenerative process that narrows or blocks arteries in the heart, brain and other parts of the body. The interior walls become lined with deposits of fat, cholesterol, fibrin, cellular waste products and calcium. These deposits form a rough, thick surface inside the blood vessels and interfere with both the smooth flow of blood and the amount of blood carried through the arteries. This narrowing of the blood vessels restricts blood flow, causing ischemia (deficiency of blood at the heart tissue due to either functional constrictions or obstructions of a blood vessel), and is the underlying pathologic condition in many forms of cardiovascular disease including CAD, aortic aneurysm, peripheral vascular disease and stroke.

In the majority of cases, the first indication of atherosclerosis is seen during exercise when the oxygen requirement of the heart muscle (myocardium) increases. Indeed, atherosclerosis is generally silent until it manifests itself as CAD, peripheral vascular disease, stroke or sudden death.

Disorders of the coronary arteries are common manifestations of atherosclerosis. CAD develops when the coronary circulation is insufficient to supply the oxygen requirements of the heart muscle, resulting in ischemia. CAD has three major clinical manifestations: angina pectoris, a condition marked by periodic episodes of chest pain, especially during exertion, that result from transient and reversible myocardial ischemia (when CAD has progressed such that it is clinically apparent, it is also referred to as ischemic heart disease); myocardial infarction, the term used to describe acute necrotic changes in the myocardium that are usually secondary to coronary occlusion (heart attacks); and sudden death, an unexpected cardiac death occurring within an hour of the onset of the heart attack, often without symptoms.

Diagnosis and evaluation of coronary artery disease is challenging to the practicing physician because myocardial ischemia occurs at irregular intervals or without pain or other symptoms. Historically, the diagnosis and management of coronary artery disease has been performed using both non-invasive and invasive procedures. Prior to 1970, the principal non-invasive techniques available for the evaluation of the patient with heart disease were a clinical examination, chest x-ray and electrocardiograph ("ECG"). If these various modalities were inadequate and clinical symptoms were present, patients were often subject to invasive techniques of cardiac catheterization, selective angiography, or both, with the resultant discomfort, risk and necessity for hospitalization. More recently, the most common non-invasive diagnostic procedure is the resting ECG. An ECG is performed with the patient at rest, and is useful for diagnosing cardiovascular disease states such arrhythmias, hypertrophy (enlargement of the heart), and evidence of an evolving or prior heart attack. However, this test is generally not sufficiently sensitive to detect coronary disease in its early stages. More recently, echocardiography and radionuclide imaging have been used for non-invasive diagnostic purposes. Echocardiography employs ultrasound to create an image of the heart, producing real time images of anatomical structures and heart wall motion. Radionuclide imaging uses radioactive agents and specialized camera equipment to create an image of the heart. Once injected into the blood stream, radionuclide imaging agents such as thallium are taken up rapidly by healthy cardiac tissue, while poorly profused tissues take up less of the tracer. Areas with less of the imaging agent indicate the presence of occluded coronary arteries or dead tissue.

While each of the primary noninvasive diagnostic techniques of ECG, echocardiography and radionuclide imaging may be performed with the patient at rest, their diagnostic value is enhanced by stressing the patients

heart. Exercise increases the heart's need for oxygen, causing healthy coronary arteries to become dilated and blood flow through these vessels to increase. Occluded arteries impede blood flow and may not accommodate the increased needs of the heart, causing ischemia. Ischemia may elicit a symptomatic response, e.g., chest pain, or may cause cardiac disfunction, e.g., abnormal heart wall motion, which can often be diagnosed by these non-invasive methods.

Currently, the most common exercise stress testing is performed with ECG monitoring. Typically, exercise stress testing is performed after a baseline resting ECG is taken. A patient is then closely monitored through a protocol of sequential levels of exercise. The Bruce protocol is the most common protocol used in the United States. It specifies the speed and level of the incline of a motor driven tread mill during a total of seven 3-minute exercise states with no rest periods. The test is stopped when any of the following occur: when the protocol is completed; when the patient reaches a pre-set heart rate goal; when the patient experiences acute discomfort; when a diagnostic change occurs in the ECG or blood pressure; or when the patient fatigues.

Despite the fact that exercise stress testing is an important method for the diagnosis of coronary artery disease, there are numerous drawbacks which limit its overall usage. A significant problem with the procedure is that exercise must be maximal in order to obtain the greatest sensitivity. In other words, for a test to be considered diagnostically revealing, either the patient must reach a level of stress that causes ischemia or the patient must complete the protocol by reaching a predetermined maximal heart rate.

The first group of patients with whom exercise stress testing cannot be used are those who are physically unable to exercise. Approximately 20 - 30% of the relevant subject population fall in this category. Often, patients

cannot exercise due to any number of causes, such as, arthritis, limb abnormalities, obesity, obstructive lung disease, peripheral vascular disease or other disfunction.

The second major class of patients incompatible with exercise stress testing are those for whom the results are inconclusive due to an inability to achieve the necessary heart rate. Again, this comprises from 20 - 30% of the subject patients.

Thirdly, exercise stress testing involving physical motion is generally incompatible with echocardiography and radionuclide imaging. With echocardiography, lung expansion and patient movement reduces the quality of the echocardiography ultrasound image. With radionuclide imaging, the image cannot be made at the moment of peak stress when diagnostic capability is greatest. Generally, the physical motion of the body caused by exercise generated stress diminishes the image quality or requires a time lapse resulting in suboptimal diagnosis.

Fourthly, exercise stress testing by physical motion is generally inconvenient to both patient and doctor. For example, a maximal stress test exhausts most patients and involves a significant recovery time. Additionally, maximal stress tests involve a degree of risks for the patient of falling which is directly related to the use of a tread mill. Because of the physical movement associated with the exercise, placement of the electrodes is also a problem. Specially designed electrodes which minimize motion artifacts must be securely attached. Finally, placing the electrodes can involve shaving the chest for a man, and sometimes burnishing the skin to achieve appropriate electrode contact.

Taken as a whole, these drawbacks make exercise stress testing an inconvenient test for both patient and physician. Because of its inherent difficulty, lack of sensitivity, lack of specificity, and cost, exercise stress testing is not generally recommended for asymptomatic individuals.

It is desirable to perform diagnosis for coronary artery disease by methods which can stress the heart in a manner which mimics aerobic activity while not forcing the patient to actually engage in strenuous physical activities. A test wherein the heart is stressed without the need for physical exercise would be not only of great practicality, but would also allow for the testing of individuals who heretofore have been unable to engage in exercise stress testing.

Various drugs exist which elicit acute and adaptive cardiovascular responses similar to the types of responses elicited by aerobic activity. They will be referred to as Exercise Simulating Agent beta agonists or "ESA™ Beta Agonists" for purposes of this invention. Generally, these drugs are catecholamines. Catecholamines are essential compounds in the body and play many important roles. For example, adrenaline and noradrenaline are natural catecholamines which act as neurotransmitters and hormones, controlling among other things, the function of the heart muscle. During physical exercise for an exercise stress test, adrenaline and noradrenaline are released, increasing the rate and force of contraction of the heart and blood pressure. These natural catecholamines do not act selectively on the heart, however, and have side effects which make them unsuitable as agents to pharmacologically stress the heart.

Several groups have described the intravenous infusion of synthetic catecholamines. In one example, United States Patent No. 3,987,200 entitled "Method for Increasing Cardiac Contractility" issued to Tuttle et al. on October 19, 1976, discloses a synthetic catecholamine dobutamine. Dobutamine elicits certain specific cardiac responses without the adverse side effects that would accompany administration of a natural catecholamine. Dobutamine exerts a positive inotropic effect (increasing heart contractility) without inducing arrhythmia and with minimal heart rate and blood pressure effects. When

infused intravenously at high doses, dobutamine elicits increases in heart rate, myocardial contractility, arterial blood pressure, and coronary and skeletal muscle blood flow. Such responses resemble the effects of physical exercise. Although the heart rate does increase with infusion of dobutamine, the drug was designed to specifically minimize this effect. Increasing heart rate is referred to as positive chronotropic effect.

More recently, the novel catecholamine analogue, arbutamine, has been developed. Arbutamine appears to act selectively on the heart and cause an increase in the rate and force of contraction of the heart and blood pressure. Arbutamine is described in detail in Tuttle et al. "Diagnosis, Evaluation and Treatment of Coronary Artery Disease by Exercise Simulation Using Closed Drug Delivery of an Exercise Simulating Agent Beta Agonist", Serial Number 308,683, incorporated by reference, above. Arbutamine is a catecholamine analog designed to stress the heart pharmacologically. Arbutamine produces a dose-dependent cardiovascular response similar to that of physical exercise. Accordingly, the heart rate can be increased incrementally by gradually increasing the amount of drug administered. Generally, the duration of action of arbutamine is short, and when drug delivery is terminated, the heart returns to a normal range of activity within a period of time similar to that which occurs after physical exercise. Tuttle et al. contemplate a closed loop drug delivery system in which the response variable (e.g., heart rate) is monitored for effect caused by the input variable (e.g., drug infusion rate). Computer control of the closed loop drug delivery is contemplated. The drug delivery device administers arbutamine to the patient, monitors the patients heart rate and optionally blood pressure, and controls the rate of drug delivery to obtain the desired heart rate. This system is advantageously useful in connection with widely used cardiac

testing procedures, such as ECG, echocardiography and radionuclide imaging.

Ordinarily, drug delivery systems are control systems having an input-response relationship. A drug input, such as an absolute amount or an infusion rate, produces a physiological response related to the input. Typically, the input (such as drug infusion rate) is used to control some parameter associated with the response variable, such as a desired rate (heart rate, blood pressure level, etc.).

Broadly speaking, drug delivery systems are either open loop delivery systems or closed loop delivery systems. An open loop drug delivery system is one in which the drug is delivered at a predetermined rate without any direct or automatic adjustment in response to physiological response variables. A closed loop drug delivery system is one in which a drug is delivered in automatic response to feedback of a physical signal or response, which could include responses such as heart rate, blood pressure, ECG parameters, heart output or other similar physical response. While numerous types of closed loop systems exist, representative categories of control schemes include: linear-nonlinear, deterministic-stochastic, and adaptive-nonadaptive. More particularly, closed loop delivery systems include predictive type and proportional-integral systems. In a predictive system, the input quantity is correlated to the difference between the current value of the response variable and the desired or target level (i.e., error term). The proportional-integral systems utilize a proportionality error term plus an integral error term, each having different contributions to the overall input amount.

Closed loop drug delivery systems have been used for therapeutic purposes to maintain a physiologic parameter. One specific example is the use of a closed loop drug delivery system to control infusion of Nipride to control a patient's blood pressure. Such a system is described in

Petre et al., "Infusion Pump Control", United States Patent No. 4,392,849. Such a system is designed to maintain stability of a physiological parameter, as opposed to variation of that parameter for diagnostic purposes. Yet further examples of closed-loop drug delivery systems for therapeutic purposes are disclosed in Newman, PCT Application WO 88/08729, entitled "Iontophoresis Drug Delivery System", published November 17, 1988. Various therapeutic closed-loop drug delivery applications are mentioned, including for medication delivery, control of blood pressure, insulin delivery and administration of pain killing drugs.

There are many unique and important obstacles presented in effective diagnosis utilizing a closed loop drug delivery system, especially for diagnosis of the heart. For example, there is potentially a long time delay for arrival of the drug at the target organ, that being the time between the administration at an intravenous or transdermal location and arrival at the heart. Secondly, it is quite often the case that various patients respond differently to a given drug, making response predictability more difficult. Third, there is the possibility of excessive build up of a drug in a patient. Fourth, safety monitoring for a contra-response must be done, and drug delivery terminated. Finally, monitoring the heart rate is a difficult signal to track as the heart rate is a very noisy signal.

Despite the clear desirability of a system which is effective in the diagnosis and management of CAD, no effective system has been known heretofore.

Summary of the Invention

A closed loop drug delivery system uses patient response and rule based decision making methods to achieve operator specified responses for diagnostic purposes. In the preferred embodiment, the system causes stress thus allowing cardiac diagnosis by administration of an exer-

cise simulating agent drug to pharmacologically stress the heart. The physiological response may be monitored by any known method, including ECG, echocardiography and radionuclide imaging. An acute cardiovascular response is achieved like that induced by physical exercise. Specifically, the results include increased heart rate, increased cardiac contractility and increased systolic blood pressure levels. As a result, increasing the heart's demand for blood and oxygen helps reveal diseased arteries which cannot supply the blood to the heart.

The overall drug delivery device consists of a hardware system and an expert, rule based, control system.

The hardware system acquires various physiological parameters of the patient and further receives operator specified information and based upon the inputs, outputs the desired rate of ESA drug infusion. In the preferred embodiment the physiological parameters are the heart rate and blood pressure, and the operator specified information is a protocol. A microprocessor based hardware system is used. While one or more processors may be used, in the preferred embodiment a data acquisition processor functions principally to receive and distribute the patient's physiological response information, a display control processor functions principally to display information and to receive user specified information, and a drug delivery processor functions principally to determine the drug delivery rate. The drug delivery processor controls a drug delivery source, such as an intravenous infusion pump or transdermal iontophoretic delivery system. Optionally, various displays may provide information to the operator, with both hard key and soft key inputs available.

The method generally consists of determining the ESA drug infusion rate by reference to various rules for various modes, such as RAMP, HOLD, TARGET, and LEVEL, and transitions between modes, such as transitioning from RAMP to HOLD, based on measured physiologic values, such as heart rate.

More particularly, the method generally comprises the following steps:

Determining the individual patient response to the drug, such as onset delay for a particular patient. Patient specific information is used in conjunction with the rule based decision making. In the preferred embodiment, an initial open loop administration of a bolus of drug based on the patient's weight generates physiologic response data from which patient dose response parameters are determined.

The user specifies the particular heart rate protocol desired. A simple protocol would consist of setting a desired maximum heart rate and the desired rate of increase in heart rate. The user may specify any desired order or combination of heart rate targets. The user additionally specifies patient specific information, such as a patient's age and weight.

During the drug delivery phase, the ESA drug is administered to cause a physiologic response. When in the RAMP mode, the rate of increase in heart rate is more important than the actual difference between the target heart rate and the present heart rate. When the heart rate is approaching the target heart rate maximum, the drug delivery is modified to achieve the heart rate target with a minimum of overshoot. In the preferred embodiment, the amount of ESA drug is reduced or eliminated prior to reaching the target heart rate maximum.

Optionally, the user may enter the HOLD mode at any time. The HOLD mode seeks to maintain the heart rate at the level existing at the time the HOLD was initiated. Preferably, the HOLD heart rate is achieved with minimum overshoot. In the preferred embodiment, when a HOLD is called, the infusion rate is dropped, followed by resumption of infusion to a rate necessary to sustain the desired heart rate.

In one aspect of this invention, a protocol comprising at least a target heart rate and a plan to achieve the heart rate are defined prior to the drug phase, and the protocol may be modified after the drug phase has begun. In this way the operator may vary the protocol during the test so as to maximize the diagnostic results.

In another important aspect of this invention, a protocol is defined which includes a target value, a plan to achieve the target value and an acceptable zone of deviation from the plan. During the drug phase, should the patient physiological variable, such as heart rate, fall outside the acceptable zone of deviation from the plan, alternate rules are followed.

In another aspect of this invention, the measured physiologic parameter is filtered prior to use in the control method. In the preferred embodiment, the heart rate measured, such as by an ECG, is sent through a low pass filter to enhance performance of the control system. More particularly, a filter with an exponential forgetting factor is used along with clipping of outliers, which enhances the signal and reduces the response of the drug administration method to noise.

In yet another aspect of this invention, various alerts and alarms are used to warn of potential hazardous conditions, or to terminate drug administration in the event of a hazard. Advantageously, the alerts and alarms include such conditions as: a sudden change in a physiologic variable, such as blood pressure or heart rate, the condition where each or a combination of the heart rate and blood pressure are in a marginal condition or excessive heart rate.

Optionally, user oriented interfaces are provided for ease of operation. In the preferred embodiment, a display system provides data on patient condition and response, as well as an indication of the user specified protocol information. A soft key system is useable with the display to provide for flexible user input.

In summary, the various modes of RAMP, LEVEL, TARGET, and HOLD, and the transitions between any of them, such as RAMP to HOLD, are controlled by a rule based, expert system based upon action of the hardware to achieve the desired physiological response. A protocol may be changed by the operator even after drug delivery has begun. Further, the control system itself will change administration rules if a patient response deviates from an acceptable zone.

Accordingly, it is a principal object of this invention to provide for improved diagnosis, prognosis and management of coronary artery disease.

It is yet a further object of this invention to provide for effective physiological stress of a patient without physical exertion of a patient.

It is an object of this invention to permit stress testing of patients who could not otherwise be tested due to an inability to exercise.

It is yet a further object of this invention to permit enhanced echocardiography and radionuclide imaging of patients under stress condition.

It is yet a further object of this invention to enhance patient safety, such as by reducing overall drug dosage.

It is yet a further object of this invention to provide a HOLD mode which achieves the desired heart rate with a minimum of overshoot, which enhances safety by not requiring a restart, thereby reducing total drug dosage, and which reduces the total testing time.

It is yet a further object of this invention to provide various alerts and alarms to enhance patient safety.

Brief Description of the Drawings

Fig. 1 is a block diagram of the overall control system.

Fig. 2 is a perspective view of the ESA device.

Fig. 3 is a graph of heart rate versus time showing various control modes.

Fig. 4 is a block diagram of the HR input filter system.

Fig. 5 shows heart rate response and infusion rate for a constant infusion of drug as a function of time.

Fig. 6 shows the heart rate and drug delivery rate as a function of time for a protocol of a RAMP to a heart rate target.

Fig. 7 shows the heart rate and drug delivery rate as a function of time for a protocol of a RAMP to a first heart rate target followed by a RAMP to a second heart rate target.

Fig. 8 shows the heart rate and drug delivery rate as a function of time for a protocol of a RAMP to a heart rate target, including a HOLD.

Fig. 9 shows the heart rate and drug delivery rate as a function of time for a protocol which revealed ischemia.

Fig. 10 is a block diagram of the hardware system.

Detailed Description of the Invention

Overview of the System and Method

Fig. 1 shows a block diagram of the ESA system 10. The ESA device 10 receives operator inputs 12, including the operator specified protocol (such as heart rate slope, heart rate hold and target heart rate) and patient information such as weight, age and gender. The ESA device 10 additionally receives physiological parameter inputs 14, such as heart rate and optionally blood pressure of the patient 15. The ESA device 10 provides various forms of outputs, including display outputs which provide information to the operator. The ESA device 10 outputs the drug 16 infusion rate or the drug itself if the drug delivery mechanism is included within the ESA device 10. Finally, the ESA device 10 outputs various alerts and

alarms to warn the user of specified conditions or to terminate drug administration.

The physiological input of measured heart rate 14 when input to the ESA device 10 goes through a heart rate filter to produce an average heart rate (HRa). At this time the alerts and alarms for irregular heart rate and unstable heart rate may be activated if appropriate. The operator inputs 12 are provided to the control system, and include the input of MODE selection. The operator input 12 also includes the desired heart rate target which, during operation, is utilized in conjunction with the computed average heart rate to generate an input to the control system. The alert for no start up differential heart rate is derived from the heart rate average and MODE selection. Additionally, the average heart rate is used for saturation detection, and the associated alert or alarm for saturation, slope estimation and patient gain estimation. These in turn are provided to the control system as inputs. Based upon these inputs to the control system, the output of the control system is used to control the infusion 16. An alert or alarm for maximum dose utilizes the output from the control system. The maximum dose rate and the maximum total dose may be monitored as desired.

Fig. 2 shows a perspective view of one design for the ESA device. A housing 20 generally includes a monitoring system, drug delivery controls and a drug delivery mechanism. In the preferred embodiment the monitoring system includes a screen 22 for display of information for the operator, system status lights 24 and soft keys 26. The display 22 is conventionally used to display an indication of the function of the soft keys 26. The drug delivery controls include various hard keys 28, which optionally include LEDs within them. The hard keys 28 may be used to enter, by way of example, the heart rate protocol (such as heart rate target, heart rate slope, or HOLD heart rate), numerical data such as a patient's age, or may cause other

actions such as alert and alarm silence. The drug delivery mechanism may consist of any known form, whether intravenous or transdermal drug delivery. In the preferred embodiment, an IV pump 30 drives a syringe 32 to deliver the ESA drug via an intravenous (IV) administration set and catheter 34. The housing contains various functional elements such as an on/off switch 36 and an AC power receptacle 38. Optionally, a data transfer port, such as an RS-232 connector 40, is included. ECG leads and non-invasive blood pressure cuff 44 are attached through the housing 20.

The drug administration method may be broadly classified into three time periods -- predrug, drug and postdrug. Fig. 3 shows a plot of heart rate versus time. The predrug, drug and postdrug periods are labelled above the graph.

The predrug time period is considered to be from when the monitoring leads 42 are attached (in the case of ECG monitoring) to start of drug administration. During this time a patient's baseline is established, principally for resting heart rate and blood pressure. During this period, the operator may enter patient related information such as age, weight and gender on the hard key pad 28. Further, the operator would specify the protocol, typically consisting of at least a heart rate target (e.g., 60 beats per minute over baseline) and the desired heart rate slope (e.g., increase of 8 beats per minute). Finally, during the predrug period the operator would typically prepare the drug syringe 32 and IV administration set and catheter 34, or if a transdermal delivery system is used, prepare the drug delivery electrodes.

In Fig. 3, the baseline heart rate is shown prior to the time T0 and the heart rate target is labelled on the y-axis and marked with a horizontal dotted line.

The drug phase begins with the initial administration of drug and ends when drug administration is stopped. An initial bolus of drug is provided to the patient, and

the patient response in heart rate monitored. During the drug phase, various operational modes exist. Among these modes are the LEVEL mode, the RAMP mode, the TARGET mode and the HOLD mode. Fig. 3 shows the LEVEL mode from time T1 to T2 and from T7 to T8, the RAMP mode from times T2 to T3, T4 to T5 and T8 to T9, the TARGET mode from T5 to T6, and the HOLD mode from time T3 to T4. The LEVEL mode occurs early in the drug cycle and is characterized by a generally uniform heart rate. The RAMP mode occurs during the drug phase and is characterized by a rate of increase in heart rate. The TARGET mode occurs during the drug phase and is characterized by a decreasing rate of heart rate increase. The HOLD mode occurs during the drug phase and is characterized by a relatively uniform heart rate. In addition to the various operational modes themselves, there are transitions from mode to mode such as from RAMP to HOLD. The drug phase is exited when the operator issues a stop or interrupt, or an alarm is generated by the ESA device, or the heart rate target is achieved.

The postdrug phase begins when drug administration ends. During this period, the heart rate and blood pressure of the patient are monitored. As shown in Fig. 3, the heart rate in the postdrug phase, T6 to T7 and after T9, decreases after drug administration ceases, in a manner not unlike heart rate response following termination of exercise.

As shown in Fig. 3, protocols may go from a postdrug phase to a further drug phase, shown at the transition time T7.

Filtering of the Measured Physiologic Parameter

The ESA device 10 receives the heart rate signal from a source, such as an ECG monitor. The measured heart rate can be a very erratic signal. Because of the large variability in the heart rate signal, a low pass filter is preferably used to extract the slower dynamics corresponding to the response of the heart rate to drug infusion.

Additionally, since the heart rate serves as the feedback signal to the control system, large or frequent outliers, that is signals falling outside an expected window around the heart rate, would introduce undesired fluctuations in the infusion rate profile. On the otherhand, excessive averaging would distort the heart rate signal and present an incorrect patient profile to the control system.

Fig. 4 shows a block diagram of the basic filtering method of the preferred embodiment. The measured heart rate HR(k) 50 represents the unfiltered signal as supplied from the patient monitoring device. The unfiltered heart rate signal HR(k) has the outliers removed 52 prior to averaging. The output of the filter circuit is the filtered average heart rate HRa(k) 54. In the preferred embodiment, the average heart rate HRa(k) 54 is derived from an averaged signal having an exponential forgetting factor. A fraction G is summed with a fraction 1 minus G of the preceding averaged heart rate signal HRa(k-1) 56. Typically, sampling is done every 5 seconds.

In the preferred embodiment, the following method and parameters have proved useful for filtering the heart rate to enhance operation of the drug administration control. To obtain the heart rate from the peak to peak interval (called "rr") measurement from the ECG signal, the following calculation is performed:

$$\overline{rr}(t+1) = \frac{7}{8} * \overline{rr}(t) + \frac{1}{8} * rr(t+1) \qquad (1).$$

The heart rate at time t is given by:

$$HR(t) = \frac{60}{\overline{rr}(t)} \qquad (2).$$

The heart rate value is updated every time a new R-wave is detected. The control system samples this HR signal every 5 seconds to acquire a new value for feedback control.

The following heart rate filtering rules were discovered based on actual test data, and generally provide for outlier clipping where a measured signal is either more than 6 beats per minute above or 8 beats per

minute below the average heart rate. The following rules have proved effective in successfully filtering input heart rate.

$$HRdiff(t+1) = HR(t+1) - HRa(t) \quad [-8 < HRdiff < 6] \quad (3)$$

$$G(t+1) = (G(t)/(1 + G(t))) + 0.04; \quad (4)$$

$$G(0) = 1$$

$$HRa(t+1) = HRa(t) + (G(t+1) * HRdiff(t+1)); \quad (5)$$

$$HRa(0) = HR(0)$$

Establishing a Baseline Heart Rate

During the predrug phase, the baseline heart rate is established. The baseline heart rate is defined as the average heart rate at the initial start of drug delivery. Fig. 3 shows the baseline heart rate as the heart rate on the y-axis prior to the time T0. In the preferred embodiment, the control method determined heart rate changes relative to the baseline heart rate. Accordingly, it is important that an accurate baseline heart rate is established.

There are several conditions which indicate that a patient's heart rate has not reached a baseline or that the control system does not have sufficient data from which to calculate the baseline heart rate. In either of these cases, a nonacceptable condition or value (such as a heart rate of zero (0)) is returned as the baseline heart rate, indicating that drug initiation must be delayed until a valid baseline heart rate has been established. In the preferred embodiment, any of the following conditions will prevent the baseline heart rate from being established:

(1) Receiving less than two minutes (24 samples) of valid ECG measurements.

(2) Presence of an excessively low heart rate, e.g., heart rate less than 26 bpm, or excessively high heart

rate, e.g., heart rate more than 120 bpm, while the baseline is being established.

(3) An ECG lead coming loose, the baseline heart rate being reset to a nonacceptable condition or value (e.g. zero heart rate) for half a minute.

(4) The existence of an "irregular heart rate" condition, which is defined to be an absolute (positive or negative) difference of more than 20 bpm between the measured heart rate and the averaged heart rate (HRa) for 2 consecutive samples.

(5) The presence of excessive noise in the measured heart rate signal, which in the preferred embodiment is measured as the variance (or sum of the square of the error between the measured heart rate around the current running average HRa). The variance is estimated using the following formula:

$$smsq(t+1) = smsq(t) + (c * ((HR(t)-HRa(t))^2 - smsq(t))) \quad (6).$$

where $smsq(0) = 20$; and $c = 0.1$

Excessive noise may indicate a problem with the ECG leads or the R-wave detection. The constant "c" determines the rate at which the estimated sum of the squares will be updated with information from newly acquired data. In the preferred embodiment, the estimate of the noise variance is not updated if any of the following conditions exists: (1) an irregular heart rate condition is detected, (2) the ECG leads are off, or (3) an uninterpretable heart rate, that is, excessively low or high heart rate, is observed. If the estimate of the noise variance exceeds 100 bpm^2, the baseline heart rate is set to a nonacceptable condition or value (e.g. zero heart rate). Optionally, if the estimate of the noise variance exceeds 200 bpm^2, an alarm is sounded.

The Drug Phase

Once a valid baseline heart rate is established and the other pre-drug phase requirements satisfied (such as

setting of protocol and establishing the drug-delivery system), the drug phase may be entered.

Drug Response

Fig. 5 shows a typical response curve of the heart rate to constant infusion of arbutamine, the ESA drug. The change in heart rate from the baseline value is shown on the y-axis on the left, and the drug infusion rate (μg/kg/min) is shown on the right hand y-axis. Drug infusion incurred at approximately time 350 and ends at approximately time 715, with a constant infusion rate of 0.25 μg/kg/min. There is an onset delay between the time drug infusion begins and a perceptible increase in heart rate is measured. The onset delay is labelled 2 in Fig. 5. Typically, the onset delay is approximately 1 minute for arbutamine. The onset time or time needed to achieve steady state heart rate corresponding to a constant infusion rate, is labelled by 3 on Fig. 5. The offset delay, the time during which heart rate continues at preexisting levels after the infusion is stopped is labelled 4 on Fig. 5. The offset delay is approximately the same as the onset delay for arbutamine. The offset region is that after the offset delay, labelled 5 in Fig. 5.

Pharmacodynamic analysis of arbutamine establishes that there is a threshold level of action to achieve heart rate response. Typically, minimum infusion rate of 0.05 μg/kg/min. is necessary to observe a change in heart rate sufficient to distinguish it from the noise level.

The Initialization Mode

The initialization mode is shown at time T0 in Fig. 3, and represents the first stage in the drug phase. At the beginning of the ESA test, an effective threshold level of drug must be established, and the onset delay overcome. In the preferred embodiment, an open loop 1 minute bolus of arbutamine is delivered at a constant infusion rate of 0.1 μg/kg/min. Based upon pharmaco-

dynamic analysis, the onset delay averaged 80 seconds, with the range being from 25 seconds minimum to 125 seconds maximum. Generally, the onset and offset delay is caused by the transport time from the point of drug administration to the heart and activation of the receptors. The pharmacodynamic studies further show that the time constant for onset to reach half maximum response value is approximately 5 minutes, whereas the offset time to decrease to half maximum is 7.5 minutes. The difference between onset and offset half maximum times is believed to be caused by a difference in association and disassociation of the drug with the beta agonist receptors of the heart.

Control in LEVEL Mode (T1)

Fig. 3 shows the LEVEL mode at time T1. After the initial bolus is delivered in the initialization mode (T0), the control method closes the feedback loop on the heart rate signal HRa and begins titrating the drug infusion. Titration begins at the 0.1 μg/kg/min. delivery rate established during the bolus administration. Initially, the control method target is set to plus 20 bpm above baseline during LEVEL control. While this start-up period is not essential, the following reasons weigh in favor of the LEVEL mode prior to beginning higher rates of drug infusion:

(1) Because of patient-to-patient variability in the onset delay, some patients may not have responded to the drug during the bolus period. If the control method target were to continually increase before a corresponding increase in heart rate occurred, an overly aggressive infusion profile could result.

(2) Because of variations in patient-to-patient gain (differential heart rate gain per unit drug infusion) the response in heart rate to the initial bolus may vary significantly. Providing a constant heart rate target during the LEVEL mode permits preliminary

estimate of the patient profile to be established. The gain is preferably used in the control method for later modes.

(3) The start-up period is selected to allow the system sufficient time to show a response to drug infusion. Because of the fixed target and the conservative control during this period, the amount of drug infused will be limited.

The Proportional-Integral Control Method

In the preferred embodiment, a proportional-integral control method is used. The simple representation of the proportional-integral formula to calculate the control U(t) in discrete form is:

$$u(t) = kp * e(t) + ki * \sum_{l=0}^{\ell=t} e(l) \qquad (7)$$

where the tracking error is:

$$e(t) = trgt(t) - HRa(t) \qquad (8)$$

with trgt being the value of the desired trajectory and ki and kp being the controller gains. The values for ki and kp for various modes is listed in Table 1.

	Level Mode	Ramp Mode	Hold Mode	Target Mode
kp	4.0	4.0	2.0	2.0
ki	0.4	0.4	1.0	1.0

TABLE 1

Equations 7 and 8 may be combined and written recursively as:

$$u(t) = u(t-1) + ki * e(t) + kp * (e(t) - e(t-1)) \qquad (9)$$

or:

$$u(t) = u(t-1) + k2 * e(t) - kp * e(t-1);$$

$$k2 = kp + ki \qquad (10)$$

Because of the input-output delay in the system, the correction terms with e(t) are added to an average of the infusion rates over the last minute (12 samples), giving the following formula for the average value of u:

$$\bar{u}(t-1:t-12) = \sum_{i=t-1}^{t-12} \alpha(i) * u(i) \qquad (11)$$

The complete proportional-integral formula for the control method is given by:

$$u(t) = \bar{u}(t-1:t-12) - k2*(HRa(t)-trgt(t)) + kp*(HRa(t-1)-trgt(t-1)) \qquad (12)$$

In the preferred embodiment, the weighing coefficient $\alpha(i)$ are selected as follows, to provide a stable but responsive infusion rate:

$$\alpha=\{0.1,\ 0.1,\ 0.1,\ 0.1,\ 0.1,\ 0.1,\ \frac{0.2}{3},\ \frac{0.2}{3},\ \frac{0.2}{3},\ \frac{0.2}{3},\ \frac{0.2}{3},\ \frac{0.2}{3},\} \qquad (13)$$

When in a mode in which the target is constant, such as in the LEVEL or HOLD mode, the proportional-integral rule may be written more simply as:

$$u(t) = \bar{u}(t-1:t-12) + kp*(HRa(t-1)-HRa(t)) + ki*(trgt(t)-HRa(t)) \qquad (14).$$

Transition from LEVEL to RAMP Mode (T2)

The transition from LEVEL to RAMP mode is shown at time T2 in Fig. 3. At this time, patients are preliminarily classified into one of three response categories. An "average" response is one in which the heart rate at the end of the start-up period (bolus plus LEVEL time, typically 4 minutes) has reached a value between 10 and 20 bpm above baseline heart rate. This "average" response is associated with an onset delay of 75 seconds or 15 time periods. A response is classified as "fast" if the patient reaches a 20 bpm increase over baseline during the start-up period. This is associated with an onset delay of 60 seconds or 12 time periods. Once a plus 20 bpm

increase in average heart rate is achieved, LEVEL mode (T1) is exited and RAMP mode (T2) is entered, even if this is before completion of the start-up period. A response is classified as "slow" if there is less than a + 10 bpm heart rate response at the end of the start-up period. A "slow" response is associated with an onset delay of 90 seconds or 18 time periods. Because the heart rate response is close to the noise LEVEL in a "slow" response, optionally an alert is initiated. The onset delay estimated in this mode is used for the remainder of the ESA test, except in the case where a restart occurs at which time the test for onset delay estimation is preferably repeated.

At the time of transition from LEVEL mode to RAMP mode, the control method heart rate trajectory (desired heart rate) is initialized at the then current average heart rate HRa. This prevents a build-up of large differences between the control method trajectory and measured response. Further, the controller gains ki and kp are selected for RAMP mode control from Table 1.

RAMP Mode Control

In the preferred embodiment, the control method attempts to match the rate of increase of heart rate to the operator specified rate of increase. While a control method based upon the absolute difference between the target heart rate and the current heart rate could be used, the possibility of excessive drug infusion rates is less when the rate of increase in heart rate is the control parameter. The proportional-integral formula given above is utilized to calculate the infusion rate to elicit a physiologic response to match the desired rate of increase in heart rate. In the preferred embodiment, the infusion rate calculations are performed every 15 seconds, and the infusion rate adjusted accordingly.

There are two primary conditions which take the control method out of the proportional-integral control

mode, those being the condition of saturation where the heart rate response is not increasing sufficiently, and over response where the heart rate is increasing too rapidly.

Saturation

In the case of saturation, it is has been observed that the increase in heart rate no longer increases or drops at higher infusion rates of arbutamine, typically around 0.3 μg/kg/min. An increased desired heart rate trajectory, combined with a saturation condition, could result in a steep increase in infusion rates if the proportional-integral control formula were to be strictly followed. A saturation detection mechanism in the control method detects saturation and alters the infusion rate, and optionally triggers an alert or alarm condition.

In the preferred embodiment, a peak detector tracks the last maximum average heart rate and the current sample index. If more than 30 seconds passes since the average heart rate exceeded the last maximum heart rate, the control method bypasses the proportional-integral formula. In such a case, the infusion rate is incremented every 30 seconds by a small amount. The control method switches back to the proportional-integral formula when the heart rate peak detector finds a new average heart rate maximum. In this way, rapid and unwanted increases in infusion rates are avoided during periods of saturation. Optionally, an alarm is sounded if an extended period of saturation persists or a decrease of 10BPM of average heart rate occurs.

Excessive Rate of Increase

To determine if an excessive rate of increase in heart rate is present, the control method periodically calculates a value roughly equal to the rate of increase of heart rate. In the preferred embodiment, an estimate of the heart rate slope is calculated every 30 seconds.

At 30 second intervals, the trailing average of the average heart rate over the last minute is calculated. The rate of increase is taken to be twice the difference between the new and old averages. If the slope exceeds the limit value for the specified rate of increase, the average infusion rate $\bar{u}(t-1:t-12)$ is scaled down according to the following formula:

$$scale = MAX(scalelimit, 1 - (slope-limit)/(2 * Desslope))$$

$$scale = MIN(1.0, scale)$$

where scalelimit is 0.97 (except the second time the estimated slope exceeds the desired slope ("Desslope") when scalelimit is 0.93), and "slope" is the actual rate of increase. Limit is set with the following table:

$4 \leq Desslope \leq 6$	(LOW)	limit = 6
$7 \leq Desslope \leq 9$	(MED)	limit = 9
$10 \leq Desslope$	(HIGH)	limit = 12

Transition Into HOLD Mode and Operation in HOLD Mode

The operator may demand a HOLD mode at any time. Because of the relatively substantial onset and offset delays for arbutamine, the drug already administered to the patient will cause an effect even after the HOLD mode command is received. In the preferred embodiment, it is desired to minimize the overshoot of the heart rate above the level for which a HOLD is desired. A smooth transition from RAMP to HOLD is desired.

Broadly, upon receipt of a HOLD, the control method decreases the drug infusion rate, often to a zero (0) infusion rate, and subsequently resumes infusion up to a rate necessary to sustain the desired heart rate level. Typically, the rate of drug infusion necessary during the RAMP mode will exceed the infusion rate necessary for a HOLD at a given heart rate, thus ordinarily, the final infusion rate is less than at the time HOLD was initiated. Preferably, the maximum duration of the HOLD mode is 5

minutes, and the minimum HOLD LEVEL is + 20 bpm above baseline.

Somewhat conflicting requirements are presented between the RAMP mode and the HOLD mode. In the RAMP mode, it is desired to increase at the selected rate of increase, so as to most quickly achieve the desired heart rate maximum. However, when a HOLD mode is initiated, it is desired to minimize overshoot and to stabilize the desired heart rate with minimal transient response. The rule based system disclosed here provides for smooth response.

In the preferred embodiment, the steps for transition from the RAMP mode to the HOLD mode are as follows:

(1) The controller gains ki and kp are set for the HOLD mode as given in Table 1.

(2) The operator selected rate of increase and the infusion rate existing immediately prior to the HOLD mode request are saved for use in transition out of the HOLD mode.

(3) The control method targets are set as follows:

If the HOLD mode is called during the RAMP mode, the control mode is set at + 4 bpm above the average heart rate HRa at the time HOLD starts. Since the average heart rate HRa lags the measured heart rate during the RAMP mode, this addition adjusts the control method target to an operator perceived level.

If the HOLD occurs during the start-up mode, the control mode target is set to the average heart rate HRa at the time the HOLD is called.

(4) The steady state infusion rate is initially calculated as follows:

The estimated infusion rate ("E") is calculated based on estimated patient gain and HOLD target level according to the following formula:

E = (HOLD HR - baseline HR)/Pgain, (15)

Where Pgain is a measure of the patient gain (see "Parameter Estimation", below).

If a RAMP mode was active for at least 2 minutes prior to the HOLD mode call, the pre-HOLD infusion rate (pHIR) is scaled relative to the estimated heart rate slope (described above) as set forth below:

$(slope+Desslope)/2 < 5$ scale = 0.9

$5 \leq (slope+Desslope)/2 < 9$ scale = 0.8

$9 \leq (slope+Desslope)/2$ scale = 0.6 (16)

The average of this value with the previously estimated infusion rate is used as the steady-state estimate of the infusion rate (R):

R = [E-(pHIR)*scale]/2 (17)

This calculated infusion is bound by the maximum infusion rate then existing.

(5) If no saturation is detected and a RAMP mode precedes HOLD, a 1 minute open-loop control is used. In the preferred embodiment, the control method adjusts the infusion rate geometrically from 0 to the steady state level over a 1 minute interval according to the following rule:

infusion = steady-state infusion * $(1.0-0.8^i)$;

i = 1,...,12 (18)

Because transitioning is from the RAMP mode, the built up momentum in the system, coupled with the sudden switch to HOLD mode, can result in some overshoot due to the offset delay inherent in the system. However, by following the above rules, the overshoot is minimized and the HOLD value achieved.

Transition Out of HOLD Mode (T4)

The transition point from the HOLD mode to the RAMP mode is shown at T4 in Fig. 3. To improve the resumption of heart rate increase to the RAMP mode, the initial

infusion rate is set to a different level. The following steps are used:

(1) The controller gains ki and kp are reset to the RAMP mode levels of Table 1.

(2) The control method target is reset to the present heart rate level HRa.

(3) The initial infusion rate is set according to the following rule:

Infusion Rate = 0.6 x (pre-HOLD infusion rate) + 0.4 x (end-HOLD infusion rate).

If the operator has decreased the desired heart rate slope by more than 3 beats per minute per minute during the HOLD, the prehold infusion factor is multiplied by 0.3 and the end HOLD factor is multiplied by 0.7.

Target Control (T5)

As the heart rate approaches the target heart rate, the control method acts to control drug administration in an attempt to avoid overshooting the heart rate target. This is typically effected by stopping infusion while the heart rate is still below the target heart rate. Because of the momentum in the system and the offset delay, the heart rate will still increase after infusion is stopped. This action may be taken according to the following rules:

(1) Once the average heart rate equals the heart rate target minus 2 times the selected slope, the control system slope is automatically set to 4 bpm per minute.

(2) The control system target is not permitted to exceed the operator selected target. If the control system target equals the operator selected target heart rate, the target mode is entered and the controller gains ki and kp are set as provided in Table 1.

Alternatively, overshoot may be reduced by imposing a rate of increase limit. For example, the maximum slope may be

set to 8BPM/min. when the average heart rate is within range such as 20BPM) of the target heart rate.

Target Achieved (T6)

Two separate criteria are used to determine whether the operator selected heart rate target has been achieved. Satisfaction of either of these criteria will terminate drug infusion and initiate a transition to the post-drug phase. The criteria are:

(1) If a measured heart rate sample exceeds the target heart rate and the next two heart rate measurements remain above the value (heart rate target minus 5 bpm), then the selected target is deemed to be achieved. The control system stops drug delivery.

(2) During the RAMP mode, the heart rate slope is calculated (described above) and as a result of this estimate, a "threshold to target" value is calculated. The following define the threshold for ranges of the average of the computed slope and the desired slope ("AVERAGE"):

if AVERAGE < 5, threshold = 5;

if 5 ≤ AVERAGE < 9, threshold = 8; and

if 9 ≤ AVERAGE, threshold =12.

When the average heart rate exceeds the value of heart rate target minus threshold target value, drug delivery is stopped and the heart rate target is deemed to have been achieved.

When in the HOLD mode, if either of these conditions exists, infusion continues but an alert is triggered if average heart rate is above the heart rate target. In this way, a HOLD mode may be entered despite its close proximity to the selected heart rate target.

Exit Drug Phase

In addition to achieving the heart rate target, a transition from drug phase to post drug phase happens upon any of the following events:

(1) activation of an alarm,

(2) the operator issues an "interrupt" or "stop",

(3) the HOLD mode exceeds 5 minutes,

(4) the average heart rate is above the heart rate target during the HOLD mode for 2 minutes.

During the post-drug phase, the infusion rate is set to 0.

Restart to LEVEL Mode Control (T7)

It is possible to transition from the post-drug phase to a second drug phase. This may occur if the operator has designated such a protocol, or has made the requests after the first protocol of ramp to target heart rate or has remedied an alarm condition.

If the post-drug phase has been less than 30 seconds, the control system merely resumes in the RAMP mode. In the preferred embodiment, the control system is initialized at the previously saved infusion rate, and the control system heart rate target is set at the present heart rate level HRa. No LEVEL mode control is activated. However, if the post-drug phase lasts more than 30 seconds, a start-up period is inserted before the RAMP mode is resumed. The start-up period is set for 3 minutes. Typically, the heart rate will be declining during this post-drug phase. The restart period is used to stop the downward decline in heart rate and to reverse the decline toward an increasing rate. A constant target is set at 10 bpm above the present average heart rate HRa when restart was initiated. A "virtual baseline" is formed since the heart rate is typically declining and, owing to the onset delay, typically would decline a few beats per minute towards the virtual baseline prior to

resuming an increase. The infusion rules for LEVEL mode after restart are as follows:

(1) If restart happens in the first 4 minutes of the test, infusion is initialized at 0.1 μg/kg/min.;

(2) Otherwise, the infusion rate is calculated from estimated patient gain and the control system target heart rate;

Infusion Rate = Target/Pgain.

(3) Calculated infusion rate is limited to the value of the previous highest infusion rate and by a rate depending on the desired heart rate slope as indicated in Table 2.

$4 \leq$ Desslope ≤ 6	limit = 0.15 μg/kg/min
$7 \leq$ Desslope ≤ 9	limit = 0.2 μg/kg/min
$10 \leq$ Desslope	limit = 0.3 μg/kg/min.

TABLE 2

Finally, all registers which kept track of various variables, such as slope duration, slope estimation, target threshold and maximum heart rate, from the prior drug phase are reset.

RAMP Control After Restart (T8)

The RAMP mode after restart is shown after time T8 in Fig. 3. The transition to RAMP mode after the LEVEL mode at restart is analogous to that described earlier for the initial drug phase. The alert and alarm functions detecting a lack of start-up responses are also reactivated. The "virtual baseline" is taken to be the reference heart rate for restart.

Parameter Estimation

An estimate of patient gain is used to calculate infusion rates at the start of a HOLD mode and at the restart. The patient gain estimate is calculated on-line from a recursive least-squares parameter fit on the pharmacodynamic model given by the following equations:

$$HRa(t+1) + \alpha HRa(t) = \beta * u(t-n_k) \qquad (17)$$

This patient gain can be related to the estimated coefficients α and β:

$$PGain = \frac{\beta}{1 + \alpha} \qquad (18)$$

Exemplary Results of Various Test Protocols

Fig. 6 through Fig. 9 show various possible test protocol sequences. All figures show the average heart rate and dosage rate as a function of time, with the average heart rate being shown as a solid line and the dose rate as the dotted line. The time is given in minutes, the heart rate in beats per minute and the infusion rate in micrograms per kilogram per minute.

Fig. 6 shows a programmed single rise to heart rate target. The assumed patient is a 60 year old male. In the preferred embodiment, the heart rate target is taken to the 136 beats per minute, calculated as .85x(220-60). The rate of increase of heart rate (slope) is set to a relatively low value of 4 bpm/min. The baseline heart rate value is established during the pre-drug phase (shown as the time before time 0). The drug delivery phase begins at time t0, with the open-loop bolus injection shown as the relatively higher injection rate. In the preferred embodiment, after one minute, the LEVEL mode is entered for which a heart rate target of +20bpm is set. Around time t=4 minutes, the heart rate has begun to rise and the RAMP mode is entered. As the heart rate rises towards the heart rate target of 136 bpm, the infusion rate also rises. At time t=19 minutes, the system determines that the average heart rate will reach the heart rate target, and accordingly, terminates the drug infusion. After drug infusion stops, the heart rate reaches the target heart rate and begins its decline back towards the baseline heart rate.

Fig. 7 shows a protocol having two heart rate rises to two different heart rate targets. Again, it is assumed that the patient is a 60 year old male and accordingly the

heart rate target would be 136 bpm. Here, it is assumed that the user adjusts the heart rate target to 115 bpm, perhaps due to suspected coronary artery disease. As was the case with the single rise to heart rate target protocol described in connection with Fig. 6, the first rise to the heart rate target of 115 bpm follows a similar pattern to time of 14 minutes. The heart rate continues to rise briefly to reach the heart rate target and then begins to decline. The second target of 136 bpm is then set and drug delivery is restarted at t=16 minutes. The rate of drug infusion at t=16 minutes is computed based upon the rules described above. The heart rate decline stops and the heart rate resumes its upward climb in a RAMP mode. At time t=23 minutes, the method has determined that the infusion is sufficient that the heart rate will achieve the second heart rate target of 136 bpm, and accordingly is terminated. The heart rate reaches the second target and begins its downward decline to the baseline rate.

Fig. 8 shows a protocol of a single rise to a target heart rate, with the addition of a HOLD mode occurring at time t=15 minutes. The initial bolus, LEVEL mode and RAMP mode occur as described as above. When the HOLD is selected at t=15 minutes, perhaps due to the suspected indication of ischemia, the infusion rate immediately drops significantly and then increases infusion rate to a level estimated to provide maintenance of the heart rate at the desired level. Once the HOLD is finished and the RAMP restarted at t=19 minutes, the infusion rate is increased according to the selection procedures described previously. The RAMP mode and TARGET mode are then completed, with the heart rate reaching the target of 136 bpm followed by subsequent decrease to the baseline.

Fig. 9 shows protocol of a single rise, in which ischemia is revealed. Again, the same assumptions are made as in the case of Fig. 6, with the same infusion rates and responses up until time approximately t=15 minutes. At that point, if the user gets an indication of

ischemia and desires to stop the test, pressing the STOP button immediately terminates this infusion (shown at t=17 minutes). While there is a slight continued rise in heart rate following termination of drug delivery, the heart rate soon begins its decrease. In the preferred embodiment, the patient is monitored for a relatively longer period following drug termination in a case revealing ischemia than in a case which does not indicate such a condition.

It will be appreciated that any useful diagnostic protocol may be used consistent with this invention. By combining RAMPs of various slope and duration, in combination with various lengths of HOLD, virtually any achievable desired heart rate may be specified as a function of time. A RAMP need not be linear, but may be any desired function of time.

Alerts & Alarms

Numerous alert and alarm criteria may be optionally implemented within the ESA device control program to detect hazardous conditions or unexpected patient responses to the drug. If an alarm is triggered during drug delivery, infusion is immediately terminated. The alarm condition remains in effect for a time period sufficient to permit the condition to dissipate, but not so long as to be annoying. In the preferred embodiment, this time is set for 30 seconds. By such a choice, should the operator elect to restart drug delivery, the 30 second time will require the restart to begin with LEVEL mode control. Alerts warn the operator of conditions that should be corrected within a short time, but do not stop drug delivery. The various alerts and alarms will be described below.

No Start-Up Increase in Heart Rate

It is necessary to verify that a patient is responding to a drug both at the beginning of the test and

after a LEVEL mode restart. A "No Increase In Heart Rate" alert is activated if:

(1) At the beginning of a drug administration the average heart rate has not reached 10 bpm above baseline after 4 minutes (1 minute bolus plus 3 minute start-up).

(2) After a restart is initiated, if the heart rate average HRa is less than the heart rate average at the beginning of restart (after 3 minutes) the alert is activated.

The alert is cleared after 30 seconds. Three minutes later, the "No Start-Up Increase In Heart Rate" alarm is activated if the average heart rate maximum has not reached 10 beats per minute above baseline in the case of initial start-up or virtual baseline in the case of restart.

Increasing IV Dose, No Increase in Heart Rate

These alerts and alarms detect saturation condition. As previously described, the saturation condition occurs when the average heart rate does not exceed the last maximum average heart rate for a predetermined period of time. Table 3 indicates the time in 5 second samples between these two events which cause an alert or alarm.

	HRmax <= 40		HRmax <= 55 HRmax > 40	HRmax > 55
	Slope <=6	Slope > 6		
Alert (T1)	24	24	18	15
Alarm (PT1/PT3)	48	36	30	24

TABLE 3

Preferably, the alert is not active during HOLD mode, start-up periods or prior to 1.5 minutes into the RAMP

mode. The alarm is also triggered by either of the following conditions:

(1) A 10 bpm drop in the average heart rate HRa from the previous maximum, or

(2) Heart rate average HRa is 15 bpm below the desired target during HOLD mode.

Optionally, an additional alarm condition may be set if the infusion rate is at maximum (typically 0.8 μg/kg/min.) and the IV dose is increasing but heart rate is not increasing. Another optional alarm condition may be set if the two alerts of 1) increasing IV dose, but no increase in heart rate and 2) falling systolic blood pressure occur at the same time. These alerts and alarms are preferably cleared 30 seconds after drug delivery is stopped.

Irregular Heart Rate

During the drug delivery and post-drug phases, the measured heart rate is compared to the averaged heart rate. If an absolute difference between the measured heart rate and the average heart rate exceeds 20 bpm, the average heart rate is stored. If the next measured heart rate again shows a difference of more than 20 bpm from the now stored averaged heart rate, the irregular heart rate alert is activated. If the alert persists for 30 seconds, the irregular heart rate alarm is activated. This advises the operator of short term irregularities in heart rate signal, such as excessive outlier values, and detects abnormal patient response to the drug. The alert is cleared whenever the difference between a new measured heart rate and the stored heart rate average is less than 20 bpm or 30 seconds has passed in the case of post-drug mode.

The Rapid Increase In Heart Rate Alert and Alarm

The rapid increase in heart rate alert is triggered if the average heart rate HRa exceeds the control system

trajectory by 10 bpm. The alarm is activated if the alert condition persists for a period of time, such as 30 seconds or the average heart rate HRa exceeds the control system target by more than 20 bpm.

The Heart Rate Not Stable Alert and Alarm

The sum of the squares variance used in the pre-drug and drug phases, described above, is monitored to verify the quality of the feedback signal. An alert is triggered if the variance exceeds 100 bpm^2, corresponding to approximately to a "noise level" of 10 bpm. The heart rate not stable alarm is activated if the variance estimate exceeds 200 bpm^2, corresponding to a "noise level" of 14 bpm. The variance is not updated if (1) an irregular heart rate alert is active, (2) the ECG leads are removed or (3) an uninterpretable heart rate has been observed, such as heart rate below 26 bpm.

Maximum IV Dose Alarm

This alarm is activated if the total amount of drug delivered over the complete period of test meets a specified amount. For arbutamine, a clinical limit of 10 $\mu g/kg$ is the upper limit. This alarm condition will not disappear until a new patient sequence is initiated. Optionally, the alarm flag may be cleared after 30 seconds to avoid undue operator irritation. However, further drug delivery is not permitted, and if attempted, a "maximum I.V. dose" alarm is reactivated.

The Heart Rate Over Target During HOLD Mode Alert

If the heart rate exceeds the operator selected maximum heart rate during a HOLD mode, drug infusion is not stopped, but the heart rate over target during HOLD alert is activated. This permits the operator to enter the HOLD mode at a level close to the maximum heart rate, but to avoid termination of drug delivery because of an erroneous heart rate target achieved due to overshoot when

entering the HOLD mode. If the alert persists for 2 minutes, the target reached flag is set, which causes drug infusion to stop and the post-drug phase to be entered.

Alarm From Combination of Alerts

Even when a single alert condition may not justify terminating drug delivery, the existence of two or more alerts may justify an alarm condition. For example, alerts relating to heart rate and to blood pressure, each of which is merely on alert, may justify an alarm. A Falling Systolic Blood Pressure Alert plus a Heart Rate Saturation Alert existing together cause an Alarm.

User Interface

The user interface is preferably designed to permit ease of operation. Graphical representations of heart rate, blood pressure and average heart rate are provided to the user, as well as numeric indications of current actual and average heart rate and blood pressure. User operated keys, optionally soft keys, permit modification of heart rate trajectory during actual testing. Further, the interface permits rapid and easy initiation of a HOLD or STOP command.

Description of the Preferred Hardware Embodiment

Hardware Specifics

The external aspects of the ESA device have been described in connection with Fig. 2. Internally, the main functional components may be grouped as follows: the data acquisition functions, the display control functions and the drug delivery control functions. The data acquisition functions serve to monitor the patient 15 (see Fig. 1) and to provide the physiological parameter information 14 to the ESA device 10. The display functional aspects provide the output display 18 plus various other formats of data output. The drug delivery control functional system

controls the drug infusion rate based upon the drug administration method described herein.

These functional aspects may be performed by any form of hardware system which achieves the desired performance and functional characteristics of this invention. Either a single or multiple processor system may be used. The system may be analog or digital, or a combination of both.

Fig. 10 shows a functional block diagram of the ESA device. In the preferred embodiment. Separate microprocessors are used for the various functional aspects of the system.

In the block diagram of Fig. 10, the data acquisition processor block 70 controls the data acquisition functions. The display control processor block 80 controls the display functions. The drug delivery processor block 90 determines the drug administration rate based upon the rules provided above.

The data acquisition processor 70 provides the interface between the patient and the overall ESA device. In the preferred embodiment, the patient is monitored for an ECG waveform through a 3 lead arrangement 72. An ECG amplifier 74 functions to drive the selected ECG lead 72, to electrically isolate the various ECG leads and to amplify the ECG signal prior to input to the data acquisition processor 70. Optionally, a non-invasive blood pressure measurement system is provided. A non-invasive blood pressure pump 76 inflates the cuff 78. Using any desired technique, the systolic and diastolic pressures are measured, and the pulse rate optionally determined. The data from the ECG amplifier 74 and non-invasive blood pressure cuff 78 are provided to the data acquisition processor 70. The data acquisition processor 70 filters the ECG signal, detects the QRS complex and calculates the heart rate. This information is then transferred to the display control processor 80. Optionally, electrical isolation of the patient monitoring connections is provided within the data acquisition processor 70.

The display control processor 80 serves the function of controlling the display and providing data transfer among the various processors. The display control processor 80 receives heart rate and blood pressure data from the data acquisition processor 70. This data is provided to the drug delivery processor 90. The display control processor 80 receives as further input from the drug delivery processor 90 the ESA drug dosage rate plus alert and alarm information. The display control processor 80 stores data for printing and, optionally, may provide real time data output via a RS-232 data port. In one of its primary functions, the display control processor 80 controls and formats the graphic display 100 to provide visual displays for the operator. An ESA trend display 102 and labelling for the soft keys 104 are driven by the display control processor 80. The display control processor 80 drives an audiotone generator 82 to warn of alert and alarm conditions. Optionally, the display control processor 80 provides a system clock fed to the data acquisition processor 70 and drug delivery processor 90 to synchronize operation. Finally, a system watch dog hardware circuit checks the display control processor 80 for proper operation.

The drug delivery processor 90 functions principally to determine the drug infusion rate as determined by the control method system. The drug delivery processor 90 receives alerts and alarms, plus heart rate and blood pressure data from the display control processor 80, plus inputs from the hard key pad 110. Additionally, the drug delivery processor 90 receives a response signal from the IV drug delivery source 120. Patient specific data is input from the hard key pad 110, which is optionally transmitted to the display control processor 80 for display. The hard key pad 110 provides the input for initial heart rate target and heart rate slope, patient specific data (such as weight and age) plus protocol adjustments such as changes to heart rate target, heart rate slope or

the HOLD mode. The drug delivery processor 90 monitors the IV drug delivery pump 122 for alerts and verifies dose rate commands. The drug delivery processor 90 drives a second audiotone generator 92 to indicate one of alerts and alarm conditions. The drug delivery processor 90 also controls the system status LEDs 106. A second watchdog hardware circuit 94 checks the drug delivery processor for proper operation.

All of the rules described above are stored in memory for use by the various processors. Any form of memory, whether solid state, magnetic or otherwise, may be used to store the program and rules.

The IV drug delivery source 120 may consist of any drug delivery apparatus consistent with the invention. In one embodiment, an intravenous drug delivery system is used. A IV syringe pump 122 controls drug administration rate by controlling motion of a syringe plunger. Preferably, the syringe is contained under an interlocked cover. The IV extension set connects the syringe to venipuncture device, not shown. In operation, the IV drug delivery source 120 provides the drug delivery processor 90 with infusion rate information.

In an alternative embodiment, a transdermal drug delivery system may be utilized. The details of a particularly useful transdermal drug delivery system are described in Apparatus and Method for Iontophoretic Transfer, Serial No. 07/471,296, Filed January 26, 1990, incorporated herein. Preferably, the drug delivery processor 90 would provide the transdermal dose commands to the transdermal drug delivery current source 130. The current source 130 then drives the drug electrode 132 with the indifferent electrode 134 providing the completion to the current circuit. Optionally, voltage and current confirmation may be provided from the transdermal drug delivery device to the drug delivery processor 90. Preferably, the transdermal drug delivery current course 130 limits the current and voltage to safe levels, such as

voltage less than 100 volts dc max and current less than 5 milliamps.

Though the invention has been described with respect to a specific preferred embodiment, many variations and modifications will immediately become apparent to those skilled in the art. It is therefore the invention that the appended claims be interpreted as broadly as possible in view of the prior art to include all such variations and modifications.

Claims

1. A method for cardiac diagnosis using an exercise simulating agent in a closed-loop drug delivery system which controls the patient heart rate comprising the steps of:

a) defining a protocol, the protocol including at least a target heart rate and a plan to achieve the target heart rate,

b) begin drug delivery to execute the protocol, and

c) modifying the protocol after drug delivery begins.

2. The method for cardiac diagnosis of claim 1 where in step c the protocol is modified by varying the target heart rate.

3. The method for cardiac diagnosis of claim 2 where in step c the protocol is modified by varying the plan.

4. The method for cardiac diagnosis of claim 1 where in step a the protocol further includes defining the desired rate of increase in patient heart rate during closed-loop delivery.

5. The method of claim 4 where in step c the protocol is modified by varying the desired rate of increase in the patient's heart rate.

6. A method for control of a patient physiological variable in a closed-loop drug delivery system comprising the steps of:

a) defining a protocol including a target value of the patient physiological variable and a plan to achieve the target value of the patient physiological variable, and an acceptable zone of deviation from the plan,

b) initiate drug delivery under a control system defined by a first set of rules,

c) monitor the patient physiological variable, and

d) change from the first set of rules to alternate rules if the patient physiological variable is outside the acceptable zone of deviation from the plan.

7. The method of claim 6 where in the patient physiological variable is the heart rate.

8. The method of claim 6 or 7 where in step d the alternate rules include an alert or alarm condition.

9. The method of claim 6 or 7 where in step d the alternate rule includes open-loop administration of the drug.

10. The method of claim 6 or 7 where the alternate rule includes a proportional-integral control.

11. The method of claim 6 or 7 where in step d the alternate rule includes a proportional-integral-derivative control.

12. The method of claim 6 or 7 where in step a the acceptable zone of deviation from plan includes definition of a maximum acceptable value for the patient physiological variable.

13. The method of claim 6 or 7 where in step a the acceptable zone of deviation from plan includes a maximum acceptable rate of increase in the patient physiological variable.

14. The method of claim 6 or 7 where in step b the control system is a proportional-integral control system.

15. The method of claim 6 or 7 where in step b the control system is a proportional-integral-derivative control system.

16. A control system for closed-loop drug delivery for diagnostic purposes comprising the steps of:

a) administering the drug,

b) monitoring the patient response to the administered drug,

c) determining the individual patient response to the administered drug, and

d) conduct diagnostic procedure with the closed-loop controller utilizing the individual patient response information.

17. The method of claim 16 where the individual patient response information includes patient gain.

18. The method of claim 16 where in the individual patient response includes an estimation of the time constant for drug response for the patient.

19. The control system of claim 16 where the individual patient response information includes the onset delay for the drug.

20. The method of claim 16 where in the drug is an exercise simulation agent used for cardiac diagnosis.

21. A method for medical diagnosis using closed-loop drug delivery and a variation of a patient physiological variable comprising the steps of:

a) specifying a desired rate of increase in the patient physiological variable,

b) administering a drug which causes variation in the patient's physiological variable,

c) monitoring the patient physiological variable,

d) determining the rate of change in the patient physiological variable, and

e) controlling the drug delivery in the closed-loop system to achieve the determined rate of change of the patient physiological variable equal to the desired rate of change in the patient physiological variable.

22. The method of claim 21 where in the patient physiological variable is heart rate.

23. The method of claim 21 where in the desired rate of change in the patient physiological variable is a positive number.

24. A method for closed-loop drug delivery for cardiac diagnosis using an exercising simulating agent drug comprising the steps of:

a) specifying a protocol, the protocol including a target heart rate,

b) establishing a baseline heart rate,

c) determining the individual patient response to the drug,

d) monitoring the heart rate,

e) administering the drug based upon predefined rules, the monitored heart rate and the individual patient response, and

f) output the results to the operator.

25. The method of claim 24 where in the protocol specifies the desired rate of increase in the heart rate.

26. The method of claim 24 where in the protocol specifies the time of hold at the target heart rate.

27. The method of claim 24 where in the protocol specifies patient specific information.

28. The method of claim 24 further including the step of establishing a baseline for the blood pressure.

29. The method of claim 24 where in step c where in the individual patient response is determined in response to an open loop administration of the drug.

30. The method of claim 24 where in the step c the determination of individual patient response includes the patient gain.

31. The method of claim 24 where in step c the determination of individual patient response includes determination of the time constants for the patient to the drug.

32. The method of claim 24 where in the monitored heart rate is average prior to use in step e.

33. The method of claim 24 further including the step of monitoring the patient blood pressure.

34. The method of claim 24 further including the step of monitoring for saturation.

35. The method of claim 24 where in step e the rules include control for a ramp mode.

36. The method of claim 24 where in step e the rules include an initialization mode.

37. The method of claim 24 where in step e the rules include a level mode.

38. The method of claim 24 where in step e the rules include a proportional-integral control method.

39. The method of claim 24 where in step f the output includes a trend plot.

40. The method of claim 24 where in step f the output includes real time data provided to the operator.

41. The method of claim 24 further including the step of issuing alerts or alarms.

42. The method of claim 24 further including the step of filtering the monitored heart rate.

43. The method of claim 24 where in step e the rules respond to receipt of a hold command.

44. A method for a achieving a RAMP mode in a closed-loop drug delivery system where the rate of drug delivery affects a physiological parameter, comprising the steps of defining a desired rate of increase in the physiologic parameter, and administering the drug at a rate so as to achieve a rate of increase in the physiologic parameter equal to the desired rate.

45. A method of claim 44 where in the physiologic parameter is the heart rate.

46. A method for achieving a HOLD mode in a closed-loop drug delivery system where the rate of drug delivery affects a physiologic parameter, comprising the steps of:

receipt of the HOLD condition,

initial reduction in the rate of drug delivery,

subsequent increase in the rate of drug delivery, such that at the end of the increase, the rate of drug delivery results in maintenance of the physiologic parameter at the desired value.

47. The method of claim 46 where in the initial reduction in the rate of drug delivery is to a zero rate of infusion.

48. The method of claim 46 in which the increase in the rate of drug is done exponentially from the rate after reduction to the rate which results in maintenance of the physiologic parameter at the desired value.

49. A filtering method for use in a closed-loop drug delivery system, where drug is administered and the physiologic parameter of the patient is monitored and used as the input to a closed-loop control system, the method comprising the steps of:

clipping outliers based upon preset limits, and

low pass filtering the physiologic parameter.

50. The filtering method of claim 50 where the patient's heart rate is the monitored physiologic parameter.

51. The filtering method of claim 50 where in outliers in the range outside of +6 and -8 beats per minute are clipped.

52. The filtering method of claim 50 where in a first fraction of the current measured value is combined with a second fraction of a value based upon previously measured values.

53. A method for detecting saturation in cardiac response to an ESA drug comprising the steps of:

sampling a signal indicative of heart rate,

monitoring for peak heart rate,

determining the length of time since the last heart rate peak was detected,

generating a signal indicative of saturation when the length of time since the last heart rate peak was detected exceeds a pre-set time limit.

54. The method of claim 28 where in the preset time limit is 30 seconds.

55. A filtering method for use in a closed-loop drug delivery system, where drug is administered and a physiological parameter of the patient is monitored and used as the input to a closed-loop control system, when in a RAMP mode, the method comprising the steps of:

measuring the physiologic parameter of the patient,

determining the slope of the physiologic parameter as a function of time,

comparing the computed slope with a threshold value, and

generating a signal indicative of saturation condition if the measured slope is less than the threshold slope.

56. A method for determining an excessive rate of increase in a cardiac diagnostic procedure comprising the steps of:

calculating a value indicative of the heart rate at a first time,

calculating a value indicative of the heart rate at a second time,

generating the difference between the two calculated values,

comparing the difference with a preset value, and

generating a signal indicative of an excessive rate of increase if the difference meets or exceeds the preset value.

57. In a closed-loop drug delivery method, where a physiologic parameter is controlled for diagnostic

purposes based upon drug administration, the improvement comprising the addition of a hold mode which permits the an operator to specify a hold mode to maintain the value of the physiologic parameter.

58. The method of claim 32 where in the physiologic parameter is the heart rate.

59. In a closed-loop drug delivery system administering an exercising simulating agent to elicit stress, where the patient heart rate is monitored in response to the administration of the drug, the improvement comprising monitoring the patient for a saturation level of the drug.

60. A method for determining when a target heart rate has been achieved in a closed-loop drug delivery system using an excessive simulating agent, comprising the steps of:

monitor the patient heart rate,

determine the patient heart rate slope,

generate a threshold to target valve based in part on the heart rate slope, and

terminate drug delivery when the patient heart rate exceeds the target heart rate minus the threshold to target value.

61. The method for determining when a target heart rate has been achieved in claim 60 where the threshold to target value is generated based upon the heart rate slope and the desired slope.

62. The method for determining when a target heart rate has been achieved of claim 61 where the threshold to target value is generated based upon the average of the heart rate slope and the desired slope.

63. A method for determining an alarm condition during a cardiac diagnostic procedure utilizing more than one alert condition, comprising the steps of:

monitoring for a first alert condition,

monitoring for a second alert condition, and

generating an alarm condition if the two alert conditions are coincident.

64. The method of claim 63 where the first alert condition is falling systolic blood pressure alert and the second alert condition is a heart rate saturation alert.

65. A drug delivery system for closed-loop administration of an exercise simulation agent for purposes of inducing cardiac stress in a patient comprising:

means for acquiring data from the patient,

including the patient heart rate,

means for controlling the drug delivery based upon the data from the patient and predefined rules,

a memory for storing the predefined rules,

a drug delivery system, and

means for interfacing with an operator of the system.

66. The drug delivery system of claim 65 where the drug delivery system includes a transdermal drug delivery electrode.

67. The drug delivery system of claim 65 where the drug delivery system includes an intravenous delivery system.

68. The drug delivery system of claim 65 where the means for acquiring data from the patient further acquires blood pressure data.

69. The drug delivery system of claim 65 where the means for interfacing with an operator of the system includes a graphic display.

70. The drug delivery system of claim 65 where the means for interfacing with an operator of the system includes a audio generator.

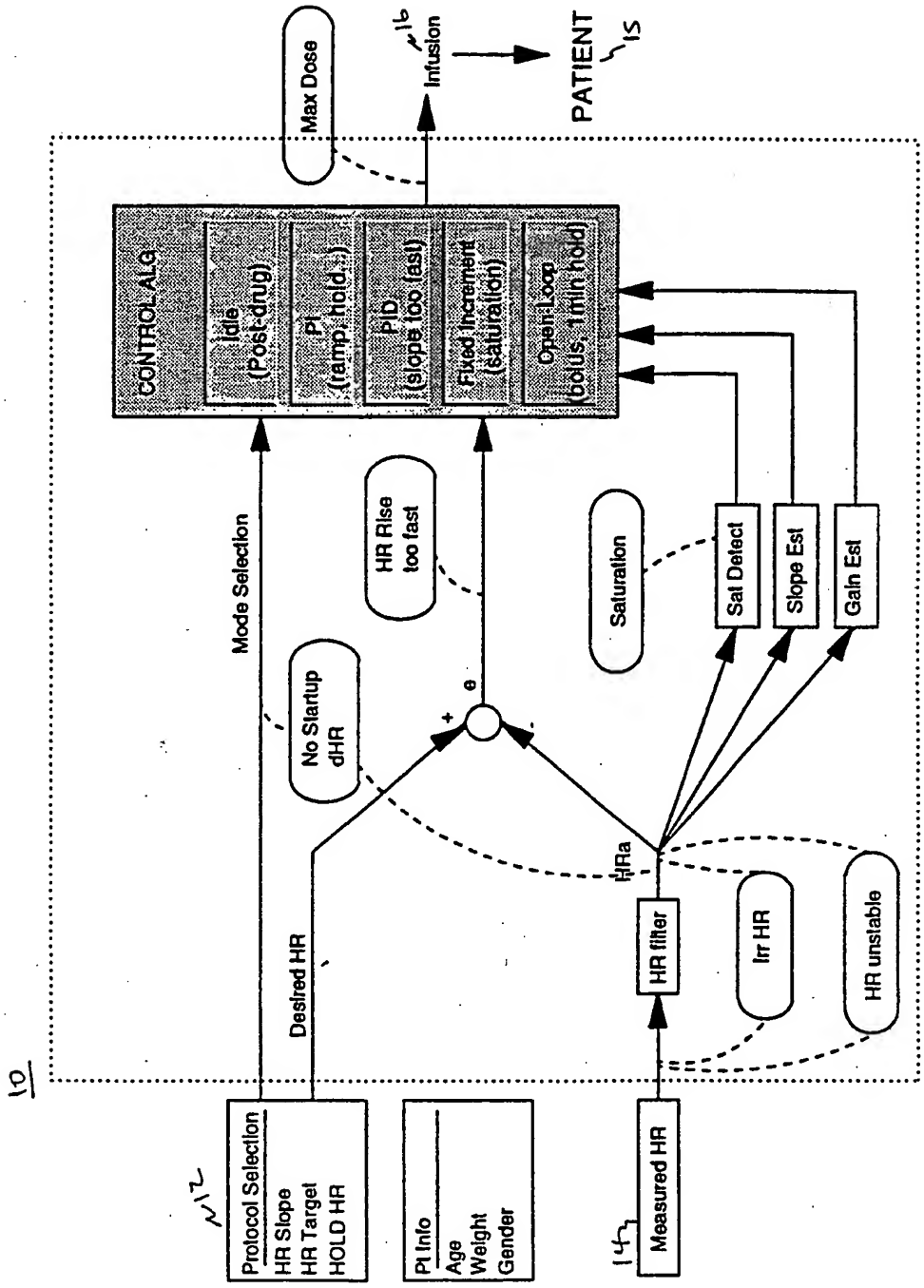
Max Dose
16
Infusion
PATIENT
15
CONTROL ALG
Idle (Post-drug)
PI (ramp, hold...)
PID (slope too fast)
Fixed Increment (saturation)
Open-Loop (bolus, 1min hold)
Mode Selection
HR Rise too fast
Saturation
Sat Detect
Slope Est
Gain Est
No Startup dHR
e
+
-
HRa
HR filter
Irr HR
HR unstable
Desired HR
10
17
Protocol Selection
HR Slope
HR Target
HOLD HR
Pt Info
Age
Weight
Gender
14
Measured HR

Fig. 1

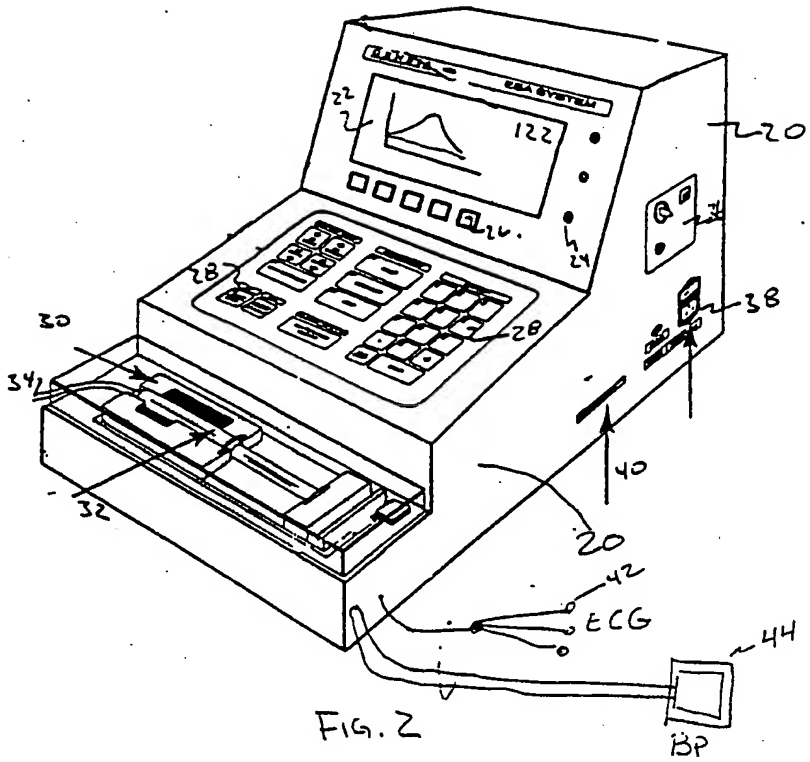

FIG. 2

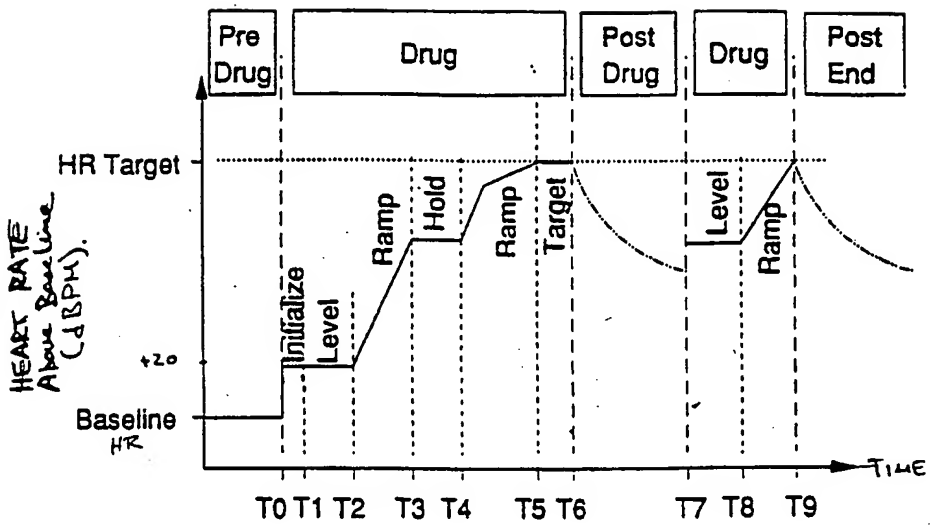
Pre Drug
Drug
Post Drug
Drug
Post End
HR Target
HEART RATE Above Baseline (dBPM).
+20
Baseline HR
Initialize
Level
Ramp
Hold
Ramp
Target
Level
Ramp
TIME
T0 T1 T2 T3 T4 T5 T6 T7 T8 T9

FIG. 3

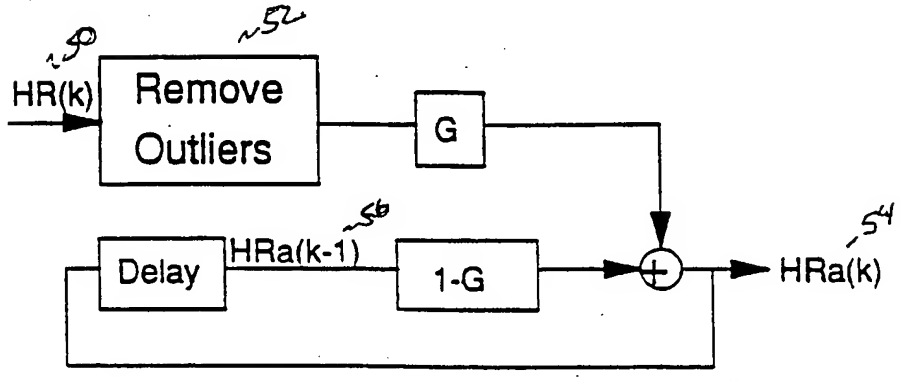
50
52
HR(k)
Remove Outliers
G
56
Delay
HRa(k-1)
1-G
54
HRa(k)

FIG 4

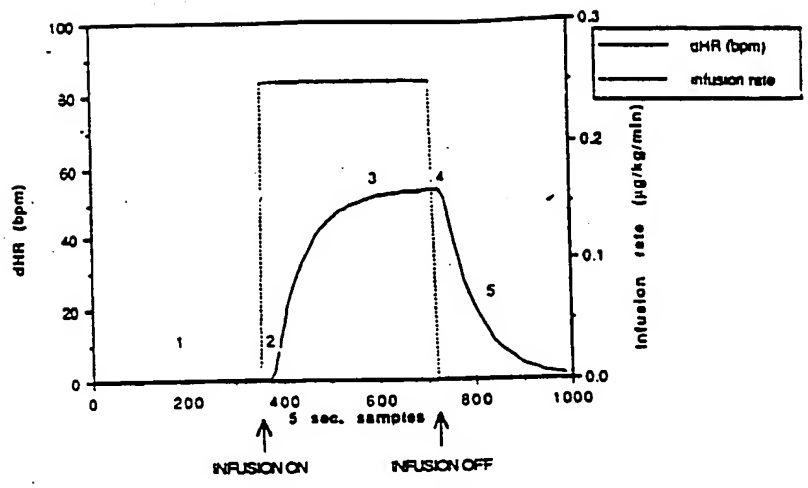
dHR (bpm)
infusion rate
100
80
60
40
20
0
0.3
0.2
0.1
0.0
Infusion rate (µg/kg/min)
1
2
3
4
5
0
200
400
600
800
1000
5 sec. samples
INFUSION ON
INFUSION OFF

FIG. 5.

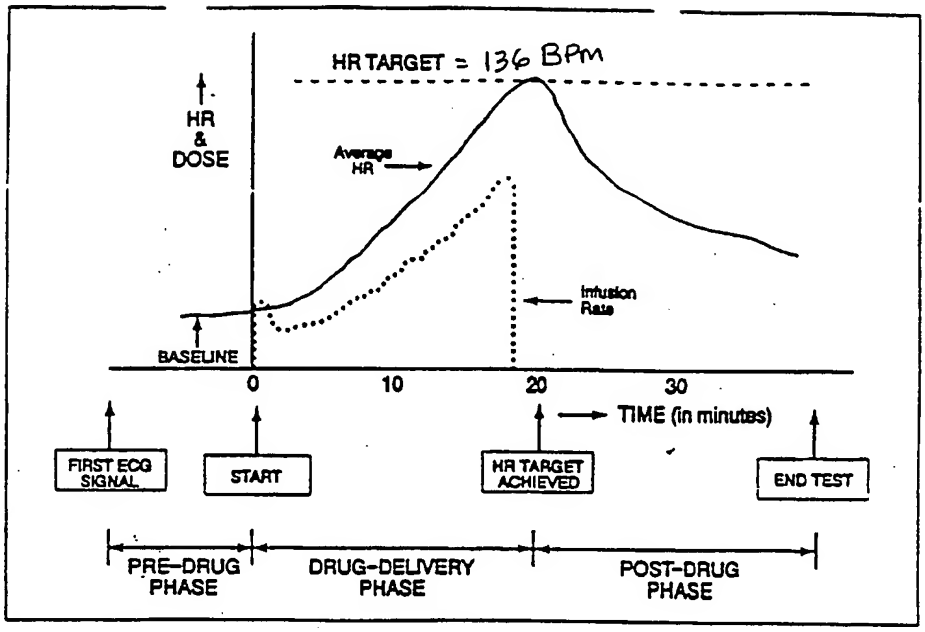
HR TARGET = 136 BPM
HR & DOSE
Average HR
Infusion Rate
BASELINE
0
10
20
30
TIME (in minutes)
FIRST ECG SIGNAL
START
HR TARGET ACHIEVED
END TEST
PRE-DRUG PHASE
DRUG-DELIVERY PHASE
POST-DRUG PHASE

Fig. 6

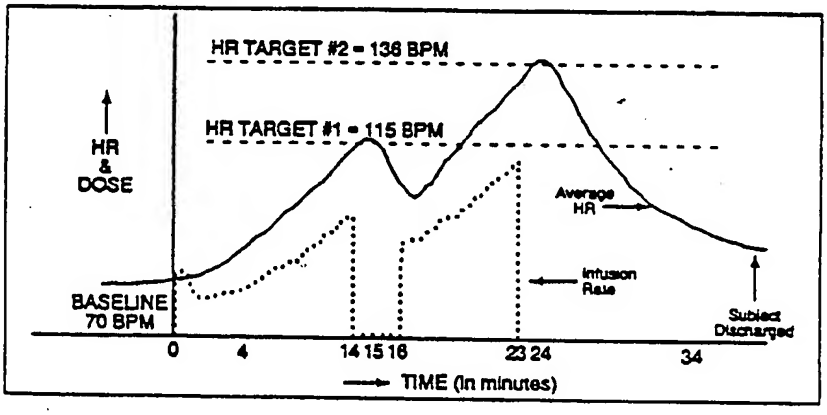
HR TARGET #2 = 136 BPM
HR TARGET #1 = 115 BPM
HR & DOSE
Average HR
Infusion Rate
BASELINE 70 BPM
Subject Discharged
0
4
14 15 16
23 24
34
TIME (In minutes)

Fig. 7

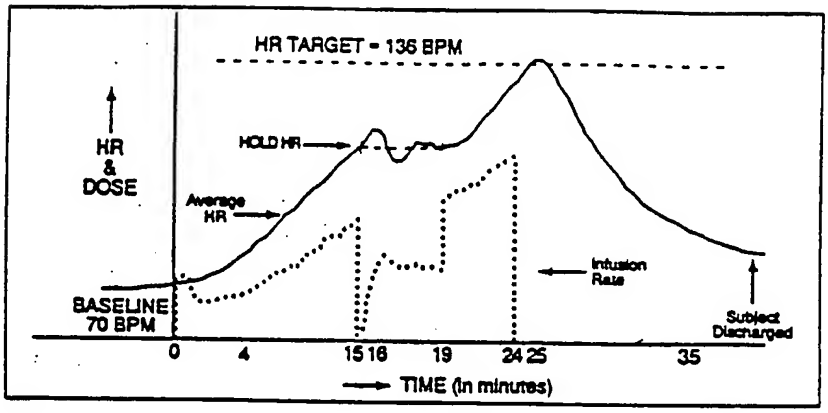
HR TARGET = 136 BPM
HR & DOSE
HOLD HR
Average HR
Infusion Rate
BASELINE 70 BPM
Subject Discharged
0
4
15 16
19
24 25
35
TIME (in minutes)

Fig. ~~8~~ 8

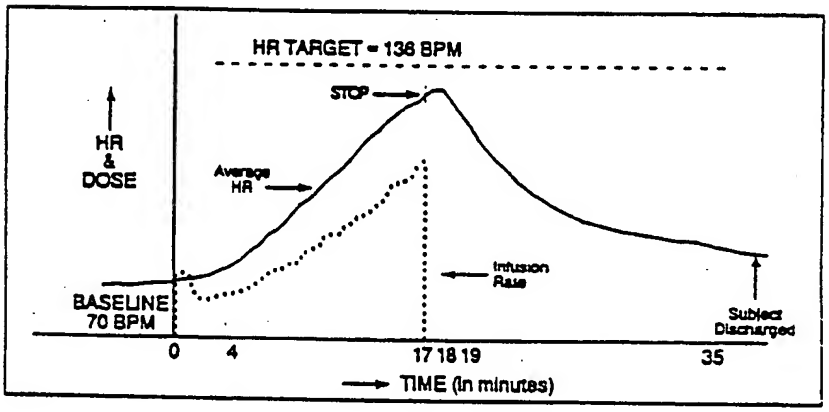
HR TARGET = 136 BPM
STOP
HR & DOSE
Average HR
Infusion Rate
BASELINE 70 BPM
Subject Discharged
0
4
17 18 19
35
TIME (in minutes)

Fig. 9

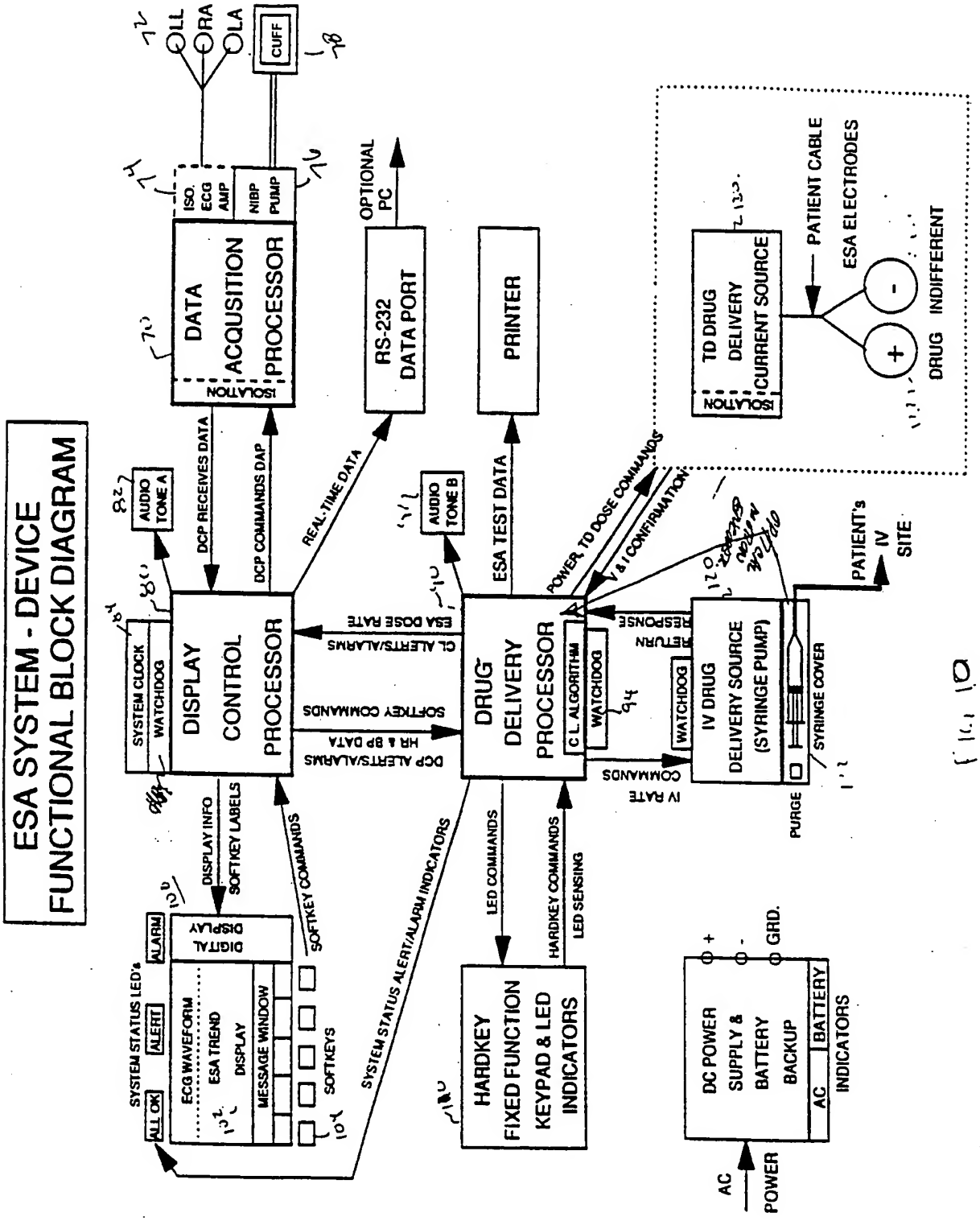
ESA SYSTEM - DEVICE FUNCTIONAL BLOCK DIAGRAM
LL
RA
LA
CUFF
ISO. ECG AMP
NIBP PUMP
DATA ACQUISITION PROCESSOR
ISOLATION
OPTIONAL PC
RS-232 DATA PORT
PRINTER
TD DRUG DELIVERY CURRENT SOURCE
ISOLATION
PATIENT CABLE
ESA ELECTRODES
DRUG INDIFFERENT
AUDIO TONE A
AUDIO TONE B
DCP RECEIVES DATA
DCP COMMANDS DAP
REAL-TIME DATA
ESA TEST DATA
POWER, TD DOSE COMMANDS
V & I CONFIRMATION
SYSTEM CLOCK
WATCHDOG
DISPLAY CONTROL PROCESSOR
ESA DOSE RATE
CL ALERTS/ALARMS
SOFTKEY COMMANDS
HR & BP DATA
DCP ALERTS/ALARMS
DRUG DELIVERY PROCESSOR
C.L. ALGORITHM
WATCHDOG
RESPONSE
RETURN
IV DRUG DELIVERY SOURCE (SYRINGE PUMP)
SYRINGE COVER
PURGE
PATIENT'S IV SITE
IV RATE
COMMANDS
DISPLAY INFO
SOFTKEY LABELS
SOFTKEY COMMANDS
SYSTEM STATUS ALERT/ALARM INDICATORS
LED COMMANDS
HARDKEY COMMANDS
LED SENSING
SYSTEM STATUS LED's
ALL OK
ALERT
ALARM
DIGITAL DISPLAY
ECG WAVEFORM
ESA TREND DISPLAY
MESSAGE WINDOW
SOFTKEYS
HARDKEY FIXED FUNCTION KEYPAD & LED INDICATORS
DC POWER SUPPLY & BATTERY BACKUP
AC
BATTERY
INDICATORS
GRD.
AC POWER

FIG. 10

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61M 31/00 | A3

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(71) Applicant: GENSIA, INC. [US/US]; 11025 Roselle Street, San Diego, CA 92121 (US).

(72) Inventors: VALCKE, Christian, Paul ; 10667 Wilkins Avenue #2, Los Angeles, CA 90024 (US). BOCHENKO, Walter, John ; 2258 9th Street, Encinitas, CA 92024 (US). HILLMAN, Robert, Steven ; 13134 Janetta Place, San Diego, CA 92130 (US).

(74) Agents: MURPHY, David, B. et al.; Lyon & Lyon, 611 West 6th Street, 34th Floor, Los Angeles, CA 90017 (US).

(81) Designated States: CA, FI, JP, NO, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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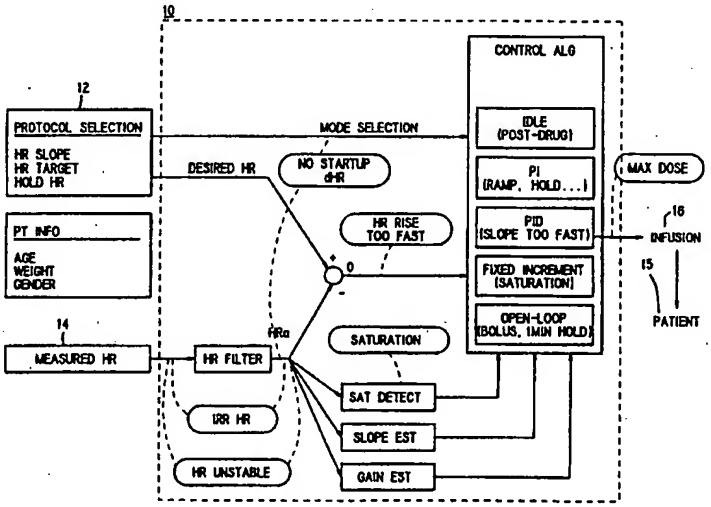
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
08 December 1994 (08.12.94)

(54) Title: METHOD AND APPARATUS FOR CLOSED LOOP DRUG DELIVERY



(57) Abstract

A closed loop drug delivery system uses patient response and rule based decision making methods to achieve operator specified responses for diagnostic purposes. Cardiac diagnosis is performed by pharmacologically stressing the heart by administration of an exercise simulating drug. A protocol is defined, which includes a target for a physiologic variable, such as heart rate, and a plan to achieve that target value. The plan includes a specification of the desired rate of increase in that variable, such as the rate of increase in the heart rate per minute. The plan comprises the desired changes in the physiologic variable as a function of time. While any desired function may be used, the more common modes include RAMP, HOLD, LEVEL and TARGET mode. The protocol may be varied by the operator after drug administration has begun. Further, the protocol includes a definition of an acceptable zone of deviation from the plan.

* (Referred to in PCT Gazette No. 03/1994, Section II)

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GA	Gabon				

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/00676

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61M 31/00
US CL :604/66
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/65-67; 128/Dig.12, Dig.13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS: Exercise (W) Stimulating (W) agent?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---, P Y	US, A, 5,108,363 (Tuttle et al.) 28 April 1992. See entire document.	1-9, 12, 13, 16-37, 39-50, 52-66 and 68-70 --- 10, 11, 14, 15, 38, 51, 67
Y	US, A, 4,871,351 (Feingold) 03 October 1989. See column 2, line 33 - column 3, line 23.	1-70
A	US, A, 4,718,891 (Lipps) 12 January 1988. See Abstract.	1-70

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
19 May 1993

Date of mailing of the international search report
25 OCT 1994

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Telephone No. (703) 308-1320

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/00676

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,551,133 (Zegers de Beyl et al.) 05 November 1985. See Abstract.	1-70
A	US, A, 4,533,346 (Cosgrove, Jr. et al.) 06 August 1985. See Abstract.	1-70
A	US, A, 4,392,849 (Petre et al.) 12 July 1983. See Abstract.	1-70

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61M 16/00 | A1

(11) International Publication Number: **WO 98/50095**

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(21) International Application Number: PCT/AU97/00278

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(71) Applicant *(for all designated States except US)*: COMPUMEDICS SLEEP PTY. LTD. [AU/AU]; 1 Marine Parade, Abbotsford, VIC 3067 (AU).

(72) Inventor; and

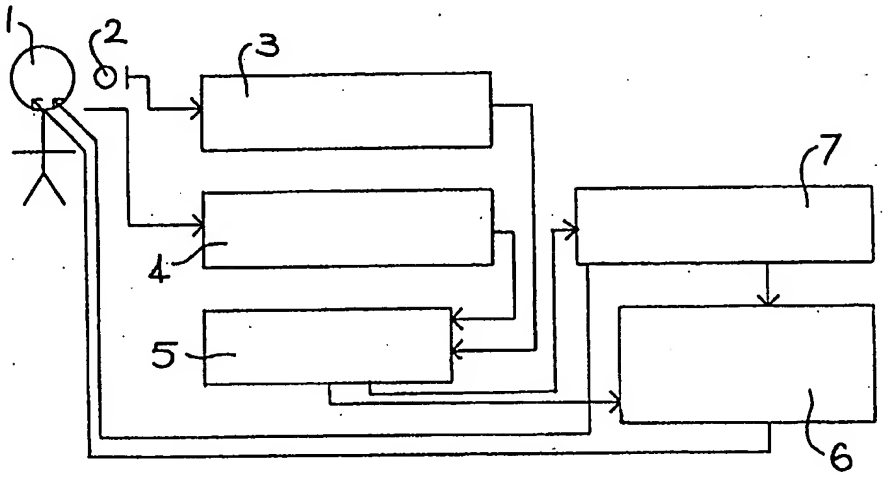
(75) Inventor/Applicant *(for US only)*: BURTON, David [AU/AU]; 62 Broadway, Camberwell, VIC 3124 (AU).

(74) Agent: PHILLIPS ORMONDE & FITZPATRICK; 367 Collins Street, Melbourne, VIC 3000 (AU).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: CONTROLLING GAS OR DRUG DELIVERY TO PATIENT



(57) Abstract

Apparatus for controlling gas or drug delivery to a patient, said delivery being adapted to maintain effective respiratory function. The apparatus includes means (2, 3, 4) for monitoring one or more physiological variables such as breathing airflow sound, EEG, EOG, EMG and/or patient position associated with the patient. The apparatus also includes means (4) for deriving from the variables, data representing a physiological state associated with the patient and means (5) for determining from the data, a gas pressure or drug quantity which substantially prevents a deterioration in the state. The determining means may include an algorithm adapted to generate a gas pressure signal which is substantially 180° out of phase relative to the phase of the patient breathing and/or sound. The apparatus may include a gas delivery means (6) for delivering gas to the patient in accordance with the determined gas pressure. The apparatus may include a drug delivery module (7) for delivering a drug to the patient.

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CONTROLLING GAS OR DRUG DELIVERY TO PATIENT

The present invention relates to apparatus for controlling gas delivery to a patient. The apparatus of the present invention is related to apparatus disclosed in applicant's copending PCT application AU96/00679 filed 31 October 1996 and in AU Patent 632932 entitled "Analysis System for physiological variables", the disclosures of which are incorporated herein by cross reference.

The apparatus of the present invention may provide a diagnostic and/or a therapeutic function. The diagnostic function may include monitoring and/or diagnosis of physiological variables associated with the patient. The therapeutic function may include application of controlled gas delivery to the patient. The diagnostic and therapeutic functions may be performed in a single device having integrated functions or it may be performed via two or more separate devices.

The apparatus of the present invention is particularly useful for investigation, diagnosis and treatment of sleep, respiratory and sleep related respiratory disorders, sleep propensity, fatigue and asthma and will be described herein in that context. Nevertheless it is to be appreciated that it is not thereby limited to such applications.

The apparatus of the present invention has been developed for, but is not limited to monitoring, analysing, storing, controlling and networking physiological variables. The aforementioned "controlling of physiological variables" includes controlling the gas delivery to a patient. This gas can be but is not limited to air as used in a CPAP (Continuous Positive Air Pressure) application, or one of the many variations of positive air pressure delivery to a patient known in the art.

Due to the complex and varying states of sleep and the broad range of sleep disorders that can be diagnosed, many different physiological variables and events can be simultaneously monitored, analysed and stored by the present

apparatus. The monitored physiological variables and events can include one or more channels of each of the following signal types:

• Breathing and snoring sounds	
• CPAP mask sound	(monitoring for patients breathing sounds within CPAP mask). These sounds include snoring, wheezing and other disordered breathing sounds
• Brain waves/Electroencephalogram	(EEG)
• Eye Movement/Electro-oculogram	(EOG)
• Muscle function/Electro-myogram	(submental EMG from muscles under the chin)
• Muscle function/Electro-myogram	(diaphragm EMG from respiratory effort)
• Muscle function/Electro-myogram	(other EMG reflecting muscle and nerve activity either by invasive or non-invasive monitoring)
• Status of patient position	
• Leg movements	(Left and/or Right legs)
• Heart beat/Electrocardiogram	(ECG)
• Oximetry	($S_a O_2$ - Oxygen saturation)
• Carbon dioxide monitoring	CO_2
• Respiratory effort	(Abdominal, thoracic or otherwise)
• Airflow	(Nasal or oral)
• Continuous Positive Airflow Pressure	(monitoring of patients mask pressure during application of CPAP treatment)
• CPAP mask temperature	(monitoring of CPAP mask air temperature for breathing activity and airflow of patient)

- Status of lights
- Graphic processing of video image (allows determination of whether patients eyes are open or closed).
- Patient digital video recording and graphic processing techniques for determination of eye lid activity (ie status of patient eyes being opened or closed - relative to fully closed or fully opened eyes status).
- Time and date stamping of monitored physiological data, video and sound.
- Infrared Video monitoring (for night studies)
- Complex sound analysis (accurate full bandwidth or limited bandwidth recording and analysis of breathing sounds. The sound is analysed and compared with criteria or a data base, consisting of reference data for disordered breathing. Microphones may be servo controlled for automatic axis adjustment to allow optimum focus on breathing sounds.)
- Physiological events: ie ECG arrhythmia, EEG spike detection, EEG spindles amongst others
- Local area networked monitoring, analysis and/or storage of a patient's physiological variables
- Endoscopy
- Breath by breath analysis-pnuemotachograph
- 3 D imaging
- Virtual patient monitoring
- Infrared eye detection for fatigue and sleep monitoring
- EEG delta and alpha-wave detection
- Eye position and movements by way of Infrared Eye Detection
- Delta Wave detections and related sleep/fatigue/impairment detection
- Mattress Device: monitoring of patient sleep state and respiratory parameters by using a mattress sensor device. The matress device can be used to monitor a patient's electro-oculogram, sleep state, arousals, position, electrocardiogram. There are presently two types commercially available mattress devices; Static Charge-sensitive Bed (SCSB) and polyvinylidene fluoride (PVDF - piezoelectric plastic).

When monitoring sleep states, sleep propensity, respiratory disorders, vigilance state or fatigue of a subject, one or more physiological variables as listed above may be continuously monitored and/or analysed and/or stored.

The present invention allows one or more channels of patient variables and/or events to be monitored, processed and recorded, while at the same time allowing precise data interconnection with a remote site. This remote site can view, process or record the real-time patient data. The communication link can take the form of a range of transmission media, including but not limited to wireless interconnection such as spread spectrum transmission wireless LAN.

The prior art provides devices for the purpose of regulating a patients breathing but these devices are unable to apply principles of acoustic cancellation as proposed by the present invention. While the applicant appreciates that prior systems can monitor patient breathing sound and in particular snoring, these earlier devices were not developed to modulate gas delivery to a patient in a way which can acoustically cancell vibration in the patient's upper palette.

According to the present invention there is provided apparatus for controlling gas delivery to a patient, said delivery being adapted to maintain effective respiratory function, said apparatus including:

means for monitoring one or more physiological variables associated with said patient;

means for deriving from said one or more variables, data representing a respiratory state associated with said patient; and

means for determining from said data, a gas pressure value which substantially prevents a deterioration in said state.

The monitoring means may include means such as a plurality of sensors and/or transducers for acquiring and monitoring variables representing physiological states associated with the patient. The physiological variables can include respiratory effort, breathing airflow, oximetry and/or sound. To this end the

monitoring means includes an air pressure wave or sound/acoustic vibration transducer to monitor breathing sound and/or air pressure waves associated with the patient's respiratory function. The air or sound pressure wave transducer may include a sound microphone, air pressure sensor, air flow sensor or similar device. The air/sound pressure wave transducer may be located near the patient such as being incorporated in the nasal or nasal and oral mask used to deliver gas to the patient, or at any other location suitable for monitoring patient airflow and/or sound. Alternatively or additionally the apparatus may include other respiratory parameters input for the purpose of monitoring and detection of respiratory effort and/or respiratory disorders.

The or each sensor and/or transducer may generate an analog signal representative of variables being monitored. The monitoring means may include means for amplifying and/or performing analog processing on the analog signal. The latter may perform filtering and/or other wave shaping functions. The processed signal may be fed to an analog to digital converter to convert the or each analog signal to a corresponding digital signal. The or each digital signal may be fed to a digital processor such a microprocessor or microcomputer. The digital processor may include software for deriving from the or each digital signal data representing the patients respiratory state. The software may include means such as an algorithm for determining from the data a gas pressure value which substantially prevents a deterioration of the respiratory state. The algorithm may be adapted to generate a gas pressure signal which is substantially 180° out of phase relative to the phase of the patient breathing air flow and/or sound together with an option of a further gas pressure signal which changes relatively slowly when compared to the out of phase signal. The latter may be used to control delivery of gas to the patient to cancel out or substantially compensate the effects of a breathing disorder. In the event that the breathing disorder is not substantially corrected the software may be adapted to activate delivery of a drug such as ventilum. This may circumvent what may otherwise be a fatal or severe asthma attack. The software may additionally be adapted to determine quantity

requirements of the drug. The latter may be based on the patients history and the extent to which the disorder fails to respond to gas pressure treatment.

A preferred embodiment of the present invention will now be described with reference to the accompanying drawings wherein:-

Figure 1 shows a block diagram of one form of gas delivery apparatus according to the present invention;

Figs. 1A to 1F show waveforms associated with the apparatus of Fig. 1;

Fig. 2 shows an overview of system software which may be used in conjunction with the apparatus shown in Fig. 1;

Figs. 3, 3A and 3B show a flow diagram of the sound and respiratory event detector /recorder;

Figs. 4 and 4A show a flow diagram of the respiratory acoustic cancellation feedback servo system; and

Fig. 5 shows one form of gas delivery system modified in accordance with the principles of the present invention.

Referring to Fig. 1 of the drawings, microphone 2 picks up sound from patient 1 and converts this to an electrical signal. The electrical signal from microphone 2 is analog in nature and is passed to signal amplifying and processing module 3.

Amplifying and processing module 3 amplifies the analog signal and performs filtering and/or wave shaping as required. The analog signal then passes to module 5. Module 5 also receives data from one or more sensors and/or transducers adapted to monitor a range of physiological variables associated with patient 1 such as respiratory effort, respiratory airflow, patient oxygen saturation,

brain waves (EEG), heart beat (ECG), eye movement (EOG) muscle function (EMG), patient position and the like. The latter are represented by module 4 which provides analog signals representing the monitored physiological variables to module 5.

Module 5 includes one or more analog to digital convertors and a digital central processing unit (CPU) such as a microprocessor or microcontroller. The CPU is loaded with software including one or more processing algorithms for generating, inter alia, a gas control signal. The gas control signal may be adapted to produce a constant or varying gas pressure and/or air flow as required to compensate a prevailing respiratory disorder.

The gas control signal is fed to pressure transducer 6 to produce a gas pressure which is of a similar frequency but is substantially 180° out of phase relative to the phase of the respiratory signal picked up by microphone 2. The antiphase gas pressure produced by pressure transducer 6 is fed to the patient 1 via a conduit such as a plastics tube and may be applied via the nasal or nasal and oral mask to substantially cancell or compensate the effect of the prevailing breathing disorder. Pressure transducer 6 may include a pressure valve for controlling gas pressure or an acoustic transducer such as a loudspeaker driver.

The apparatus optionally includes a drug delivery module 7 for delivering a drug such as ventilum to patient 1 directly or via the gas feed associated with pressure transducer 6. Drug delivery module 7 receives its control signal from the digital processing unit of module 5. The signal to initiate drug delivery may be based on a consideration of a large number of patient variables available to module 5 via module 4.

Referring to Figs. 1A to 1F, Fig. 1A shows typical sound pressure waveforms associated with a snoring patient. The sound pressure waveforms impinge upon microphone 2. Successive bursts of waveforms are shown separated by a time

"t". Where the time "t" is greater than about 10 seconds this may be interpreted by module 5 of the apparatus as an apnea episode.

Fig. 1B shows the analog electrical signal at the output of microphone 2 which is inputted to amplifying and processing module 3 in Fig. 1.

Fig. 1C shows the (analog) gas control signal outputted by module 5 and inputted to module 6 in Fig. 1.

Fig. 1D shows the actual airflow/ pressure associated with the gas (air) delivered via a conduit from module 6 to patient 1.

Fig. 1E shows the sound pressure waveform of Fig. 1A in which the (horizontal) time axis has been expanded by a factor of 10.

Fig. 1F shows the actual airflow/pressure of Fig. 1D in which the (horizontal) time axis has been expanded by a factor of 10.

A comparison of the waveforms Figs. 1E and 1F shows that at time t_1 a peak in the waveform of Fig. 1E is accompanied by a trough in the waveform of Fig. 1F, illustrating the phase reversal which gives rise to acoustical cancellation and compensates the effects of a prevailing breathing disorder.

Referring to Fig. 2 of the drawings, a combination of the following processes can be operated in real-time either individually or concurrently at any time.

(a) Sound and respiratory event detector/recorder.
(b) Sound and respiratory event detector/recorder replay system.
(c) Acoustic feedback servo system.

The following is a description of each mode of operation with reference to a typical application, being snore detection.

BLOCK 1

Block 1 represents the start of the system processes. Start can be initiated by selecting start recording from system control. Alternatively start process can be initiated by configuring the system to start at a predefined time or the device can be started automatically on power up of the apparatus.

BLOCK 2

Sound and respiratory event detector/recorder

Block 2 represents the system's event detection and recording function mode. The apparatus may be used with minimal memory requirements, in which case the processing capabilities of the system to detect and record the occurrence and frequency of events such as snoring, allows a basic detection device.

For example, the apparatus may be used to monitor patient's breathing sounds and record the events for purpose of a snore index which may allow a physician to determine the extent to which a patient is snoring. The apparatus may detect the frequency and severity (by way of amplitude or sound level measurement) of snoring by a patient. This is the simplest operation mode of the apparatus as memory requirements are minimal. The original sound does not need to be recorded and the apparatus is set up to detect snore events only and count them per unit time such as each hour, for example. By providing to a medical practitioner an indication of how many snores per hour are detected, and the sound level of these snores, the patient can be recommended for further more advanced diagnosis and/or treatment if required.

Alternatively the apparatus can be operated in a mode to store raw data from the input microphone and/or other input sensor(s). This mode of operation can be operated in conjunction with the simpler above mentioned detection mode to allow the medical practitioner to detect a patient's breathing disorders such as

snoring, while at the same time, provide a means of allowing the practitioner to review the patient raw data and validate the detection accuracy of the apparatus.

The former method of detection without the raw data recording function has the advantage of providing a lower cost device in that the memory requirements are less where the device only has to record the occurrence of an event and the time of this occurrence, as opposed to the recording of all the original raw data from the input signal(s).

BLOCK 3

Respiratory Acoustic Cancellation Feedback Servo System (RACFSS)

RACFSS represents a mode of operation which allows the monitoring of a patients breathing sounds such as snoring, while at the same time generating a control signal to provide a modulated gas delivery to a subject. The phase and airflow of the modulated gas delivery to the patient is related to the monitored sound signal from the patient. This is because snoring, due to vibration of the patient's upper palette, can be cancelled out or nulled out by way of an acoustic or pressure waveform of opposite polarity to the original sound source. In the example of snoring, vibration of the upper palette is counteracted by a pressure modulating the patient's palette in opposite polarity to the sound pressure waveforms originating the patient's snoring. This "opposite polarity" pressure or acoustic cancellation can be applied to the patient by way of a nasal mask or full nasal and oral mask. The delivery of the modulated gas to the patient is preferably such that the patient's breathing is stablilised with a minimum amount of gas.

The signal monitored from the patient can be sound, airflow, respiratory effort or other means of detecting the patient breathing.

This control of gas delivery is able to "track" the sound monitored from a patient in such a manner that sound pressure waves produced from the physiological

effects of snoring (for example) can be cancelled out by applying a base pressure with a modulated pressure signal of opposite acoustic phase to the originating patient's snore sound.

While the prior art includes Continuous Positive Air Pressure (CPAP) devices (Sullivan), Variable Positive Air Pressure devices (VPAP), Demand Positive Pressure devices, Autoset (designed by ResMed to automatically adjust CPAP pressure), the apparatus of the present invention is able to apply a modulated pressure waveform with a fast dynamic range and frequency together with a base line pressure, in order to provide acoustic cancellation of patient physiological sounds such as snoring. This type of gas delivery device requires application of unique pressure drivers such as a diaphragm in order to apply the modulation at a frequency high enough to acoustically cancel out a patients snoring with minimal modulated air pressure/flow and minimal base level pressure.

The process of Block 3 can operate individually or in combination with the processes of block 2 or block 4. When Block 3 is operated as an individual process the system is used in a mode of therapeutic control whereupon a subject can be treated for disorders such as apnea, snoring, hypopnea, amongst others.

BLOCK 4

Sound and respiratory event detector/recorder replay system

Block 4 represents the systems capability to provide a means to review:

a) ***monitored raw data*** input from the microphone;

b) review ***events detected by the apparatus*** in order to validate the precision and accuracy of event detection capabilities of the apparatus. This function is helpful to provide to a user of the apparatus a level of validation supporting any diagnostic decision that evolves from the use of the apparatus;

c) ***Selective or random sample event storage.*** This mode of operation allows the apparatus to store one or more selective or random samples of detected events. While only a limited set of raw data samples are stored, all events

may be detected, counted and summarised in terms of events per unit time eg. per hour. This technique may reduce storage requirements significantly while still providing a means for validating a recorded event by recording one or more typical detected events. An example where this function would be useful is where a patient is monitored for snoring but where false detections through excessive background noise could be indicated by allowing the user to review some sample recorded events, which may include excessive background noise, and indicate that the system results should be observed with caution.

* * *

A flow diagram associated with operation of Block 2 (sound and respiratory event detector/recorder) in Fig. 2 is shown in Figs. 3, 3A and 3B. With reference to Figs. 3, 3A and 3B the following is a description of the steps associated with Block 2.

STEP 1

Step 1 represents the system start which could be operated by selecting power on, the pre-programming of a particular start-time, by applying power to the apparatus or alternatively by remote start command.

STEP 2

Step 2 represents converting of data from the input source to a digital format so that this can be further processed in digital mode by the central processing unit of the apparatus. This input data can be, but is not limited to the input from a microphone. Alternatively or additionally the input data can be from other means of detecting patient breathing which could be for example from; an airflow sensor such as a thermistor breathing sensor, thermo-coupler breathing sensor, respiratory effort sensors, sounds recorded from a patient breathing mask (nasal or nasal and oral), a vibration sensor device attached to the patient or other means of monitoring the patient's breathing sounds or physiology.

STEP 3

Step 3 represents primary processing capabilities of the apparatus including the following:

Breathe by Breathe detection

Breathe by breathe analysis allows the "zero crossing" of each breathing cycle to be detected in order to separately classify each patient's breathing cycle. Classifying each breathing cycle allows secondary and tertiary analysis to compare a current patient breathing cycle with a previous breathing cycles in order to determine any change in characteristics of the patient breathing. This is a necessary function when determining whether the application of RACFSS is having the desired affect in relation to stabilising the patient's breathing, ie. is the application of increased and/or modulated air pressure or airflow by way of nasal breathing mask removing the symptoms of snoring, or is the application of ventilum by way of face mask removing the symptoms of asthma (ie is wheezing subsiding). Both these examples are direct applications of RACFSS.

Spectral Analysis (SA)

SA provides a breakdown of the frequency spectrum in terms of amplitude and frequency bands. This type of analysis can also incorporate amplitude or half-period-amplitude analysis. The sample period for spectral analysis can be varied within the processing stages to determine both recognition of instantaneous breathing sound changes and longer term breathing sound changes. The parameters by which the SA processing variables are configured are determined by the user of the apparatus or preset from clinical studies.

Fast Fourier transform (FFT)

FFT is a conventional form of analysis and is provided for the purpose of determining the power monitored at various frequencies. The sample period for the FFT can be varied within the processing stages to determine both recognition

of instantaneous breathing sound changes and longer term breathing sound changes. The parameters by which the FFT processing variables are configured are determined by the user or the apparatus or preset from clinical studies.

Amplitude Determination Analysis

Amplitude of the input microphone signal can be determined for the following conditions;

each period amplitude

each ½ period amplitude

average amplitude over various time intervals (ie . ½ second, 1 second, 5 seconds, 10 seconds, 20 seconds, 30 seconds, 1 minute, 5 minutes).

running average amplitude- ie average level recalculated after each new ½ period or period of monitored signal where the interval for average amplitude can be ½ second, 1 second, 5 seconds, 10 seconds, 20 seconds, 30 seconds, 1 minute, 5 minutes or other durations.

The period over which the signal average is determined can be configured by the user of the apparatus or preset from clinical studies.

Signal to Noise Analysis

Signal to noise analysis can determine normal system noise by shorting out input stage electronics and removing external sound, in order to calibrate the system for external noise against system electronic noise. Advanced signal to noise analysis can also distinguish, in part, patient breathing sounds against unwanted room noise. The determination of background noise can allow accurate threshold calculation in order to precisely set a point at which microphone signal should be ignored.

STEP 4

Step 4 represents an optional capability of the apparatus to store monitored patient data together with primary analysis data onto permanent or semi-permanent devices such as hard disk or removable flash disk devices. This

function is indicated as optional because the apparatus can be configured with no or minimal permanent or semi-permanent storage capabilities in order to reduce the manufacturing cost of the apparatus.

This type of storage is necessary to ensure that raw data from the monitored patient input can be reviewed either remotely or locally during the systems operation or at a later time. The reviewing of the data can be required by the physician or user of the apparatus. A review of this raw data allows a validation of the type of information monitored by the apparatus and also allows the apparatus to indicate to the user where and what events were detected. Thus the user of the apparatus can validate the detection algorithms and processing capability of the apparatus, which is an important factor in the use of the apparatus for providing reliable patient diagnosis.

If, for example, the apparatus is used in noisy environments the number of false event detections may increase and render operation of the apparatus unacceptable. This may be determined by viewing the recorded data and noting whether any events were undetected or falsely detected by utilising an experienced person's capability in scrutinising system performance.

STEP 5

Step 5 represents the system's RAM which can be used to store various processing requirements of the apparatus, together with minimal data storage requirements such as the detection of events, the frequency of detection of events (ie events per hour), random or selective storage of events, patient identification, amongst other storage requirements.

STEP 6

Step 6 represents secondary processing capabilities of the apparatus. This includes an ability to review the output of the primary analysis determined in step

3 above and stored in step 4 and/or 5. The various primary output data needs to be correlated with each type of secondary analysis in order to provide a more accurate means of identifying valid secondary physiological events. For example the recognition of longer term physiological breathing patterns as distinct from shorter term and irregular environmental noise provides a basis of more accurate detection than detections involving less processing and having less discriminatory detection capabilities.

Valid Physiological Breathing Sounds

Valid "physiological breathing sounds" refers to sound recorded from the patient as opposed to back ground electronic system noise and background room noise. Signal to Noise analysis (step 3) deals with calibration of system noise while the calibration of room noise against physiological noise is more complex due to the cast variety of possible room noise. "Physiological breathing sounds" refers to normal breathing sounds and various disordered breathing sounds such as snoring, wheezing, caughing, amongst others. Physiological breathing sounds may be, determined by comparing actual data (refer outputs marked A, B, C, D, F in Fig. 3) to prestored data that characterise various breathing and sleep disorders. The prestored data can be determined by comprehensive clinical trials.

Real-Time Breathe by breathe analysis (frequency and amplitude)

Breathe by breathe frequency analysis can be analysis classification of each breathing cycle in terms of amplitude, spectral and/or fast fourier transform data. These frequency and amplitude characteristics as determined for each breathing cycle (where each breathing cycle is detected in step 6 above) are then collated in terms of frequency and amplitude characterisation for each and every breathing cycle. By characterising each breathing cycle in this manner it is possible to provide a level of background noise discrimination (environmental and electronic system noise). This noise discrimination is possible as breathing noises can be related to the peak and trough points of the breathing cycle, for example. Background noise will not be associated with the breathing cycle as will

physiological breathing noises. This is an example of how noise discrimination can be implemented within step 6.

Environmental sound

Environmental noise is the total sound recorded minus the electronic signal noise and the physiological breathing sounds.

A "patient's sleep state" can be determined by the apparatus by simple means such as arousal detection. These arousal detections can be by way of monitoring additional channels such as movements from a special sensitive mattress. The mattress may be a piezo ceramic or capacitive discharge type. In both these aforementioned mattress types the apparatus is able to monitor the frequency, amplitude and regularity of patient body movements as an indicator as to whether or not the patient is likely to be asleep.

STEP 7

Step 7 represents tertiary processing capabilities of the apparatus. This includes a final analysis by referencing the information from step 6 (which determines valid physiological events as opposed to background and system noise- secondary analysis) and categorises the physiological event data into categories as recognised by medical physicians in the determination of a patients respiratory disorder or sleep disorder diagnosis.

This categorisation can include recognition of an apnea event. The latter is typically recognised by a lapse in breathing during a "patient's sleep state" for a period greater than 10 seconds. In the context of the present invention this could be recognised by detection of snoring sounds punctuated by relative breathing silence for 10 seconds or greater. This type of analysis and categorisation can provide a means of presenting a snoring index or number of snores per hour. The number of snores per hour is recognised by the medical user of the

apparatus as an indicator that the patient is suffering from Obstructive Sleep Apnea for example.

By comparing the patient's current and context (ie the context of the current sound amplitude and frequency with respect to previous sound characteristics) sound amplitude and frequency characteristics with the reference data base characterising various breathing disorders, accurate classification of patient's respiratory disorder is possible. Common, but often under-diagnosed disorders such as asthma can be detected effectively with a simple representation of the present invention by allowing the sound analysis to detect wheezing as could be characteristic of asthma or asthma onset. Wheezing, for example, can be characterised by a pre-stored set of parameters which represent typical characteristics expected when a wheezing signal is detected. These typical wheezing parameters are determined by clinical studies. This technique of comparing a currently monitored patient signal characteristics with the signal characteristics from a range of typical parameters from a sample of respiratory disorders, assists the apparatus of the present invention to provide quick and accurate detection of a number of respiratory disorders with minimal channels required for monitoring (ie in the most common implementation of RACFSS, a simple microphone channel).

Step 7 also has the function of comparing each patient's breathing cycle with a data base of patient breathing characteristics. This data-base of breathing characteristics which may be derived from prior clinical studies, allows matching of frequency and amplitude characteristics of various breathing disorders. In this way a comparison of the current patient's frequency and amplitude characteristics with a known data base of characteristics and associated disorders may assist in accurate diagnosis of the patient's breathing disorders. For example, if the patient is wheezing, the frequency and amplitude characteristics of this sound analysis is likely to match with the reference data base for a diagnostic classification of wheezing, which together with other patient states may lead to the diagnosis of asthma. This diagnosis may lead to the delivery of ventilum.

The output state or event in this case could be high level wheezing. In this example of wheezing RACFSS could be replaced with a ventilum delivery device as the feedback element. The application of ventilum to the patient as the feedback element to cancel out the acoustic symptom of wheezing manifests itself as a precise and accurate method of delivering the absolute minimum but highly responsive treatment of wheezing-related asthma.

The ventilum track algorithm could, for example (in a therapeutic mode of the apparatus) increase or decrease ventilum delivery to the patient until the wheezing state ceases. The optimum value of ventilum delivery could then be stored into a diagnostic ventilum set look-up-table (for later diagnostic reference by the supervising medical practitioner). Various values for ventilum delivery could therefore be determined in this way having regard to each patient state or breathing event.

STEP 8

Step 8 represents a capability of apparatus to store the monitored event type (ie snoring, wheezing, apnea), event time, event duration into hard disk, flash disk or other permanent or semi-permanent storage type.

This function may be optional because as noted above the apparatus can be configured with no or minimal permanent or semi-permanent storage capabilities in order to reduce the manufacturing cost of the apparatus. A review of this raw data allows a validation of the type of information monitored by the apparatus and also allows the apparatus to indicate to the user where and what events were detected. Thus the user of the system can validate the detection algorithms and processing capability of the apparatus, which is an important factor in the use of the apparatus for providing reliable patient diagnosis.

STEP 9

Step 9 represents the system's RAM or other permanent storage facility which can be used to store various processing requirements of the apparatus, together with minimal data storage requirements such temporary storage of tertiary analysis results. Temporary storage can be suitable for the purpose of providing to the user of the apparatus, a means of having a summary of the patient diagnosis. This diagnosis in the simplest form could be, for example, a snoring index (eg. snores per hour).

STEP 10

Step 10 provides "Stop Record" mode. This is achieved by detecting whether the system has a valid pre-programmed stop time, whether the system has been selected for off or whether the system power has been switched off.

STEP 11

Step 11 ends the process and follows step 10 system off selection.

* * *

A flow diagram associated with operation of Block 3 (respiratory acoustic cancellation feedback servo system - RACFSS) in Fig. 2 is shown in Figs. 4 and 4A. With reference to Figs. 4 and 4A, the following is a description of the steps associated with Block 3.

STEP 1

Step 1 represents the system start which could be operated by selecting power on, the pre-programming of a particular start-time, by applying power to the apparatus or alternatively by remote start command.

STEP 2

Step 1 represents the function of the device which detects the system user's selection of therapeutic mode. The selection of therapeutic mode is optional and allows the system to provide control for a gas delivery device, while at the same time providing detection and monitoring of respiratory disorders. The therapeutic function may not be required where the apparatus is to be used as an indicator of snoring or apnea but would be required where the apparatus is to be used for the purpose of monitoring sound while at the same time providing gas delivery control utilising the acoustic cancellation capabilities of the apparatus.

STEP 3

Step 3 analyses input data including microphone input data. The input data is analysed by reviewing the primary, secondary and tertiary results as detailed in the flow diagram of figure 3.

It is necessary to determine whether an event such as snoring has commenced in order to prepare the apparatus to operate in RACFSS mode.

STEP 4

Step 4 decides whether a respiratory event or the start of a respiratory event is detected. The apparatus will prepare itself to track the signal amplitude detected from a respiratory event in order to be able to produce a control signal for the purpose of physiological event cancellation by way of gas delivery.

STEP 5

Step 5 produces the control signal for the purpose of providing an appropriate base level pressure and modulated pressure.

This control signal contains both a base level or low frequency pressure or airflow control and a higher frequency modulated pressure or airflow control. The apparatus produces the control signal for controlling an external device. Alternatively the apparatus could be integrated into a gas delivery device which provides the capability to regulate the pressure or airflow to a patients face mask (ie nasal or full mask).

This pressure control can be similar in frequency and opposite in phase to the original acoustic waves as detected by the microphone. The apparatus should have sufficient processing capability to produce this opposite phase air flow modulation together with a base pressure in order to cancel out physiological events such as snoring with a minimum pressure applied to the patient (ie by way of nasal mask). It is desirable to keep the delivery of pressure to the patient at a minimum in order to minimise the discomfort to the patient and also to minimise side effects from therapeutic intervention by way of gas delivery.

The apparatus of the present invention is unique in its ability to produce a servo loop effect in the application of patient gas delivery. By modulating and controlling the base pressure delivery to minimise the sound monitored during snoring episodes (due to the patient's vibrating upper palette), the apparatus may apply a precise amount of opposite phase modulated pressure to stabilise the vibrating upper palette. The apparatus can provide the combination of base pressure and modulated pressure waveforms by utilising conventional technology to produce a continuous or slowly varying (low frequency) gas delivery - such as a range of pressure (say 0 CMH20 to 20 CMH20 range) with variation of rate of pressure or airflow change from say continuous to 10 cycles per second. At the same time the apparatus may provide a higher frequency modulated gas delivery - such as a range of pressure (say 0 CMH20 to 3 CMH20 range) with variation of rate of pressure or airflow change from say .5 cycles per second to say 1000 cycles per second. The apparatus of the present invention may provide these two forms of gas delivery, being continuous and higher frequency gas modulation. In one form the latter may be provided by means of a diaphragm (similar to the

cone of the driver of an audio loudspeaker) to modulate the low frequency or continuous gas delivery obtainable from a conventional respiratory ventilator or air delivery blower device. One example of the manner in which a continuous gas delivery system may be modified in accordance with the principles of the present invention is described below with reference to Fig. 5.

STEP 6

High frequency pressure rate changes and low frequency base pressure changes may be continuously checked by the system control so as not to exceed pre-programmed patient safety limits. These pressure limits may be detected and checked by way of two methods;

1) System control may limit the amount of base pressure and modulation control output from the system in order to not exceed preset patient limits.
2) The apparatus may monitor gas delivery to the patient by way of a pressure or airflow sensor interfaced to the patients breathing. This interface can be by way of a sensor attached to the patient's breathing mask, for example. The monitored airflow or pressure may be limited by the apparatus to fall within safe patient limits as reprogrammed by the system or the system user (supervising medical practitioner).

STEP 7

Step 7 functions to correct any excessive pressure or airflow modulation to remain within safe patient limits.

STEP 8

Step 8 compares microphone signal's current data with the microphone signal's previous data and determines through processes of comparing alignment and subtraction, whether activated pressure changes are having an effect on the amplitude of the respiratory event. That is, is the effect of pressure activation

change causing the current respiratory event (ie snoring sound) to reduce in presence as measured by a decrease in the amplitude of the sound signal. Reference may be had to the example waveforms shown in Figures 1A to 1F.

STEP 9

Step 9 determines whether pressure or airflow change activation reduce the effect of the respiratory event, ie does snoring subside.

The purpose of this step is to determine whether or not the application of a change of pressure and airflow to the patient is directly related to reducing the symptoms of the patient's respiratory disorder.

STEP 10

Has system "Stop Record" mode or has system pre-programmed stop time been selected or has system power been interrupted or switched off ?

STEP 11

Step 11 ends the process and follows step 10 system off selection.

* * *

Fig. 5 shows one example whereby a continuous gas delivery system can be modified in accordance with the principles of the present invention. Modification is by means of a T section element 50 inserted into the supply of base or continuous pressure or airflow 51 associated with the system. The modification comprises an air pressure modulator 52 (refer module 6 in Fig. 1) placed in communication with the leg of T section element 50 such that air pressure changes produced by modulator 52 are impressed upon the base or continuous pressure or airflow 51 to form a composite pressure/air flow 53. Composite flow 53 comprises a combination of base pressure 51 and modulated pressure/airflow produced via modulator 52. The air pressure changes impressed via modulator

52 are generally of a substantially higher frequency than changes that may be produced by the continuous gas delivery system.

Finally, it is to be understood that various alterations, modifications and/or additions may be introduced into the constructions and arrangements of parts previously described without departing from the spirit or ambit of the invention.

CLAIMS

1. Apparatus for controlling gas delivery to a patient, said delivery being adapted to maintain effective respiratory function, said apparatus including:

means for monitoring one or more physiological variables associated with said patient;

means for deriving from said one or more variables, data representing a respiratory state associated with said patient; and

means for determining from said data, a gas pressure value which substantially prevents a deterioration in said state.

2. Apparatus according to claim 1 wherein said physiological variables include breathing airflow and/or sound.

3. Apparatus according to claim 2 wherein said determining means includes an algorithm adapted to generate a gas pressure signal which is substantially 180° out of phase relative to the phase of said patient breathing and/or sound.

4. Apparatus according to claim 2 wherein said gas pressure value includes a modulated component.

5. Apparatus according to claim 4 wherein said modulated component is of opposite acoustic phase to said patient breathing and/or sound.

6. Apparatus according to claim 4 or 5 wherein said modulated component is adapted to acoustically cancell vibration in the patient's upper palette.

7. Apparatus according to any one of claims 4 to 6 wherein said gas pressure value includes a substantially continuous component and/or a component which changes relatively slowly when compared to said modulated component.

8. Apparatus according to any one of the preceding claims wherein said physiological variables include one or more of brainwaves, heart beat, muscle function and/or patient position.

9. Apparatus according to any one of the preceding claims wherein at least one of said means for deriving and said means for determining is provided via digital processing means.

10. Apparatus according to any one of the preceding claims wherein said deriving means includes an algorithm.

11. Apparatus according to any one of the preceeding claims wherein said deriving means includes means for evaluating sleep and/or arousal states.

12. Apparatus according to any one of the preceeding claims wherein said deriving means includes means for detecting micro arousals.

13. Apparatus according to any one of the preceeding claims wherein said deriving means includes means for detecting respiratory events.

14. Apparatus according to any one of the preceeding claims including a gas delivery means for delivering gas to said patient in accordance with said determined gas pressure.

15. Apparatus according to claim 11 wherein said gas delivery means include a gas pressure valve.

16. Apparatus according to claim 11 wherein said gas delivery means includes an acoustic transducer such as a loudspeaker driver.

17. Apparatus according to any one of the preceeding claims including means for delivering a drug such as ventilum to said patient.

18. Apparatus for controlling drug delivery to a patient, said delivery being adapted to maintain effective respiratory function, said apparatus including:

means for monitoring one or more physiological variables associated with said patient;

means for deriving from said one or more variables, data representing a respiratory state associated with said patient; and

means for determining from said data, a drug quantity which substantially prevents a deterioration in said state.

19. Apparatus according to claim 18 wherein said physiological variables include breathing airflow and/or sound.

20. Apparatus according to claim 18 or 19 wherein said drug includes ventilum.

21. A method for controlling gas delivery to a patient, said delivery being adapted to maintain effective respiratory function, said method including the steps of:

monitoring one or more physiological variables associated with said patient;

deriving from said one or more variables, data representing a respiratory state associated with said patient; and

determining from said data, a gas pressure value which substantially prevents a deterioration in said state.

22. A method according to claim 21 wherein said physiological variables include breathing airflow and/or sound.

23. A method according to claim 22 wherein said determining step includes an algorithm adapted to generate a gas pressure signal which is substantially 180° out of phase relative to the phase of said patient breathing and/or sound.

24. A method according to claim 22 wherein said gas pressure value includes a modulated component.

25. A method according to claim 24 wherein said modulated component is of opposite acoustic phase to said patient breathing and/or sound.

26. A method according to claim 24 or 25 wherein said modulated component is adapted to acoustically cancell vibration in the patient's upper palette.

27. A method according to any one of the preceding claims wherein said gas pressure value include a substantially continuous component.

28. A method according to any one of claims 21 to 27 wherein said physiological variables include one or more of brainwaves, heart beat, muscle function and/or patient position.

29. Apparatus for controlling gas delivery to a patient substantially as herein described with reference to the accompanying drawings.

30. A method for controlling gas delivery to a patient substantially as herein described with reference to the accompanying drawings.

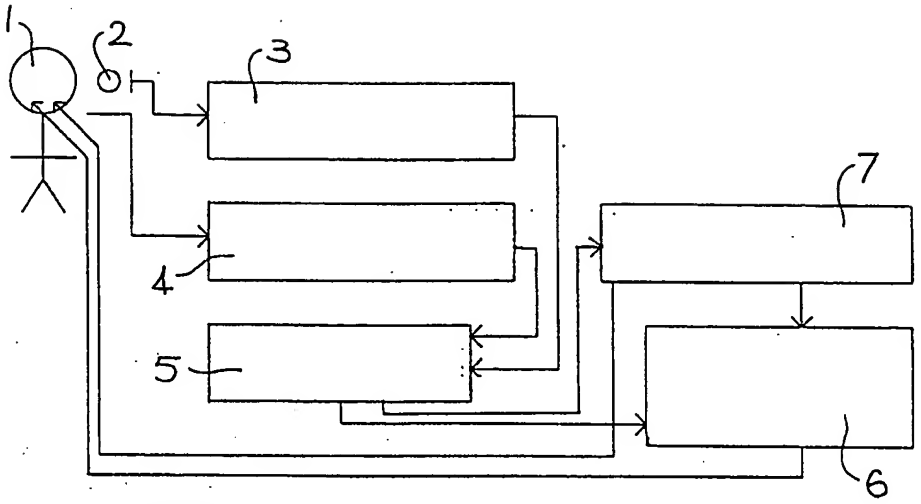
1
2
3
4
5
6
7

FIG 1

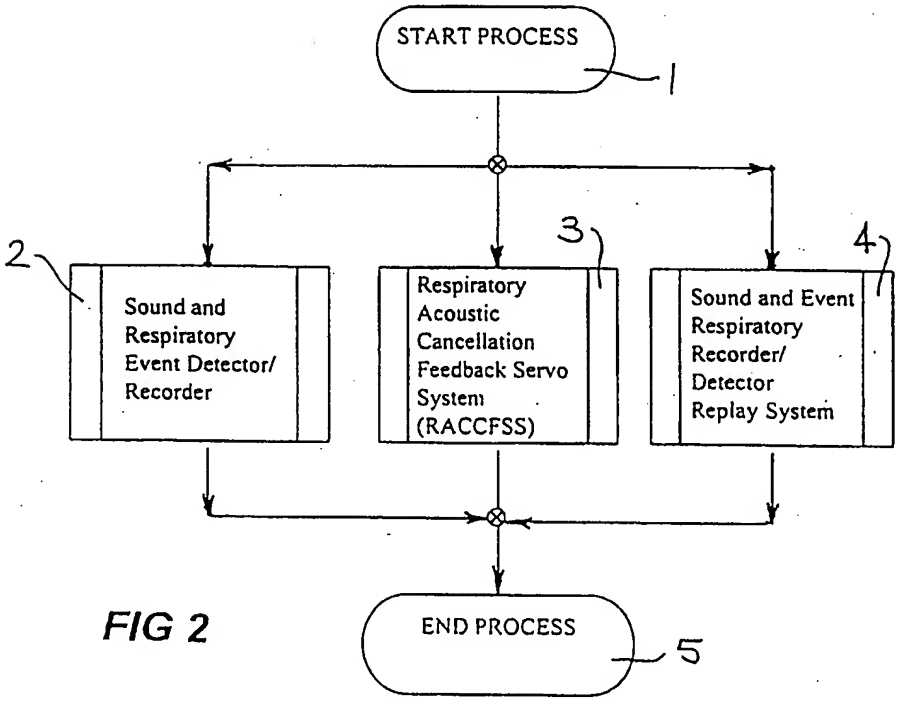
START PROCESS
1
2
Sound and Respiratory Event Detector/ Recorder
3
Respiratory Acoustic Cancellation Feedback Servo System (RACCFSS)
4
Sound and Event Respiratory Recorder/ Detector Replay System
END PROCESS
5

FIG 2

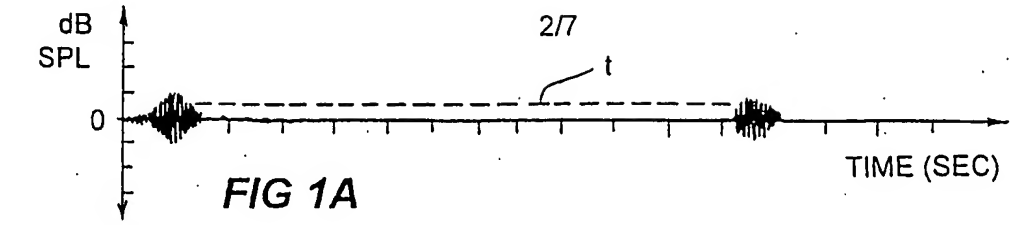

FIG 1A

FIG 1B

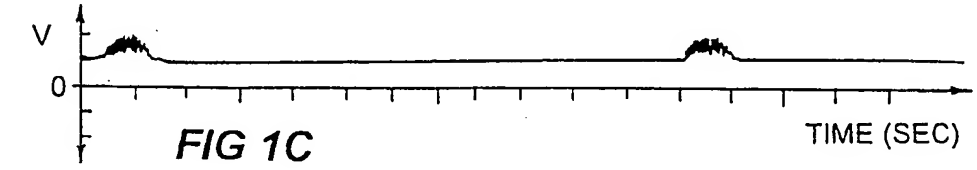

FIG 1C

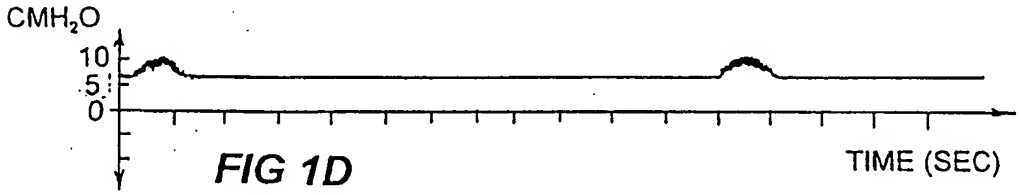

FIG 1D

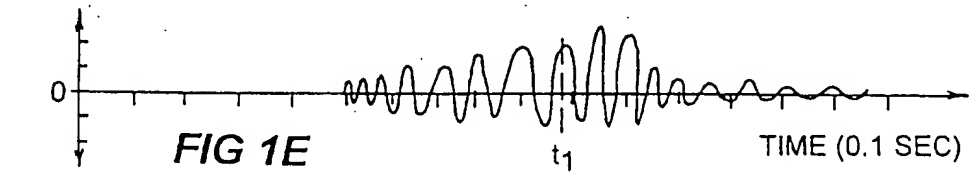

FIG 1E

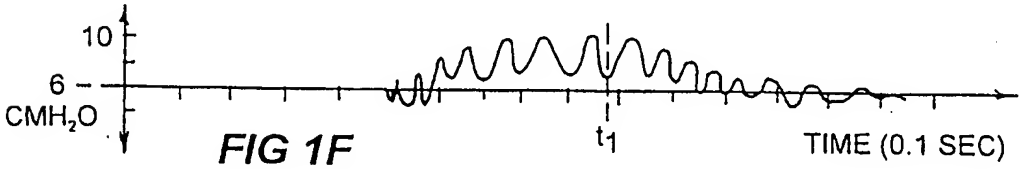

FIG 1F

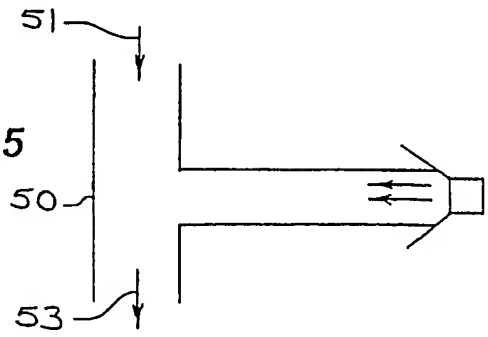

FIG 5

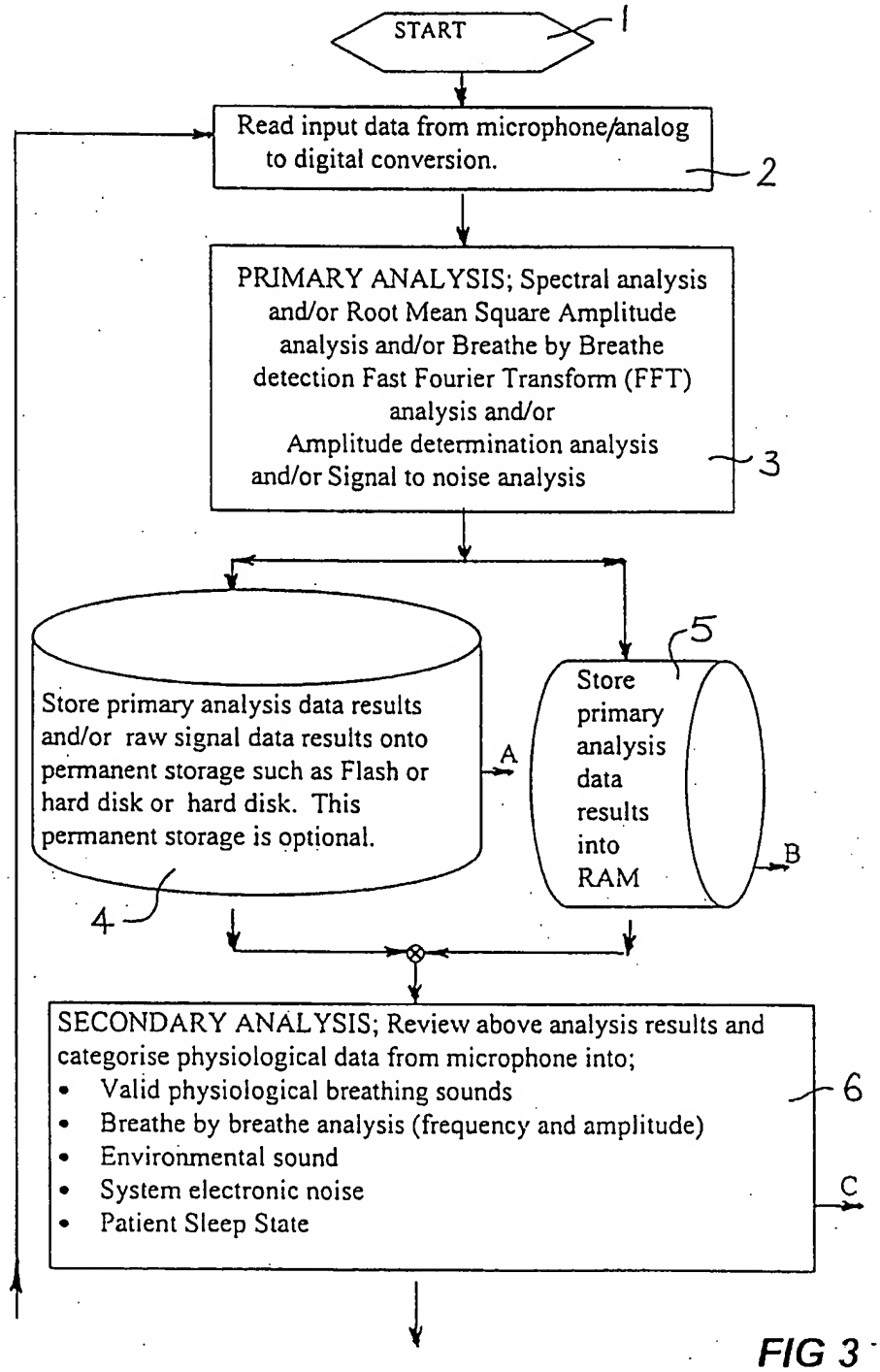
START
1
Read input data from microphone/analog to digital conversion.
2
PRIMARY ANALYSIS; Spectral analysis and/or Root Mean Square Amplitude analysis and/or Breathe by Breathe detection Fast Fourier Transform (FFT) analysis and/or Amplitude determination analysis and/or Signal to noise analysis
3
Store primary analysis data results and/or raw signal data results onto permanent storage such as Flash or hard disk or hard disk. This permanent storage is optional.
4
A
5
Store primary analysis data results into RAM
B
SECONDARY ANALYSIS; Review above analysis results and categorise physiological data from microphone into;
• Valid physiological breathing sounds
• Breathe by breathe analysis (frequency and amplitude)
• Environmental sound
• System electronic noise
• Patient Sleep State
6
C

FIG 3

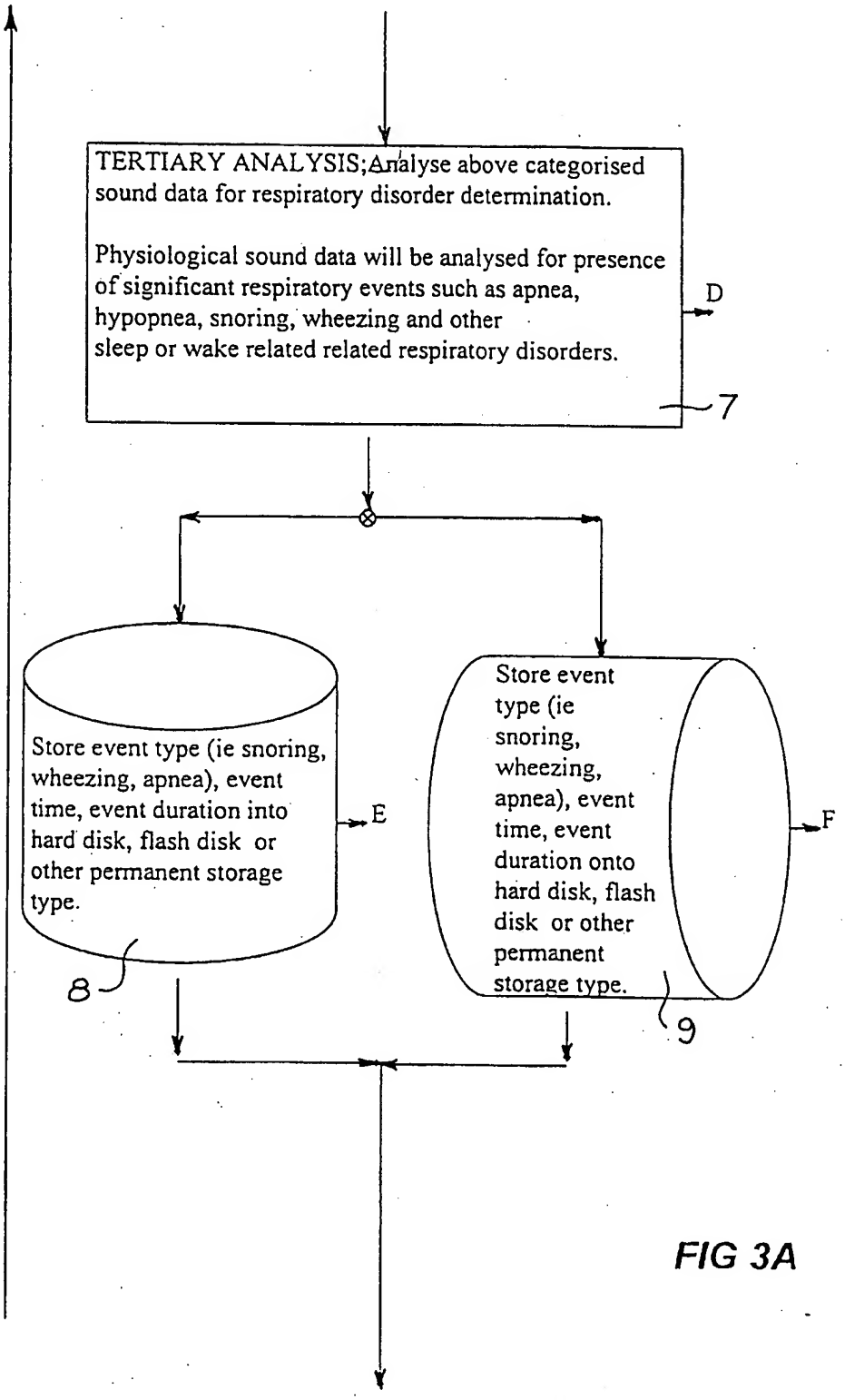
TERTIARY ANALYSIS;Analyse above categorised sound data for respiratory disorder determination.
Physiological sound data will be analysed for presence of significant respiratory events such as apnea, hypopnea, snoring, wheezing and other sleep or wake related related respiratory disorders.
D
7
Store event type (ie snoring, wheezing, apnea), event time, event duration into hard disk, flash disk or other permanent storage type.
E
8
Store event type (ie snoring, wheezing, apnea), event time, event duration onto hard disk, flash disk or other permanent storage type.
F
9

FIG 3A

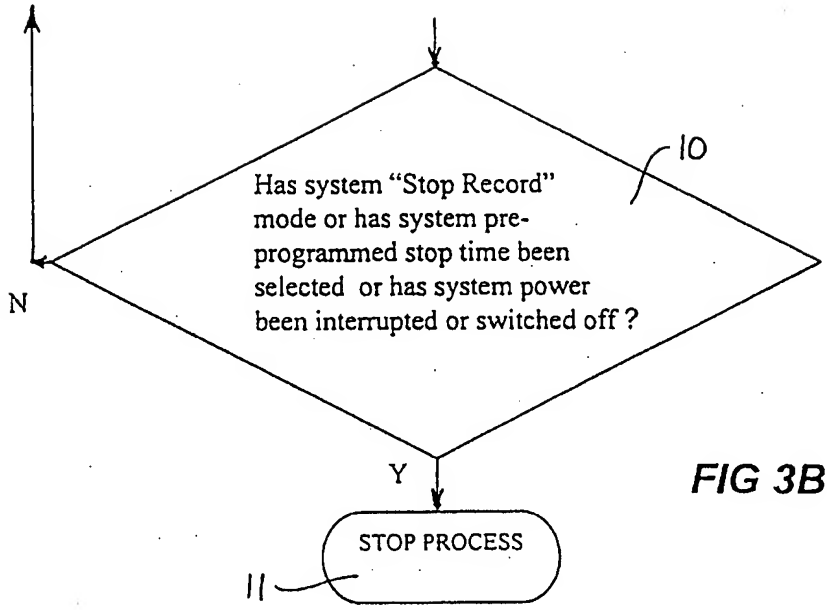
Has system "Stop Record" mode or has system pre-programmed stop time been selected or has system power been interrupted or switched off ?
10
N
Y
STOP PROCESS
11

FIG 3B

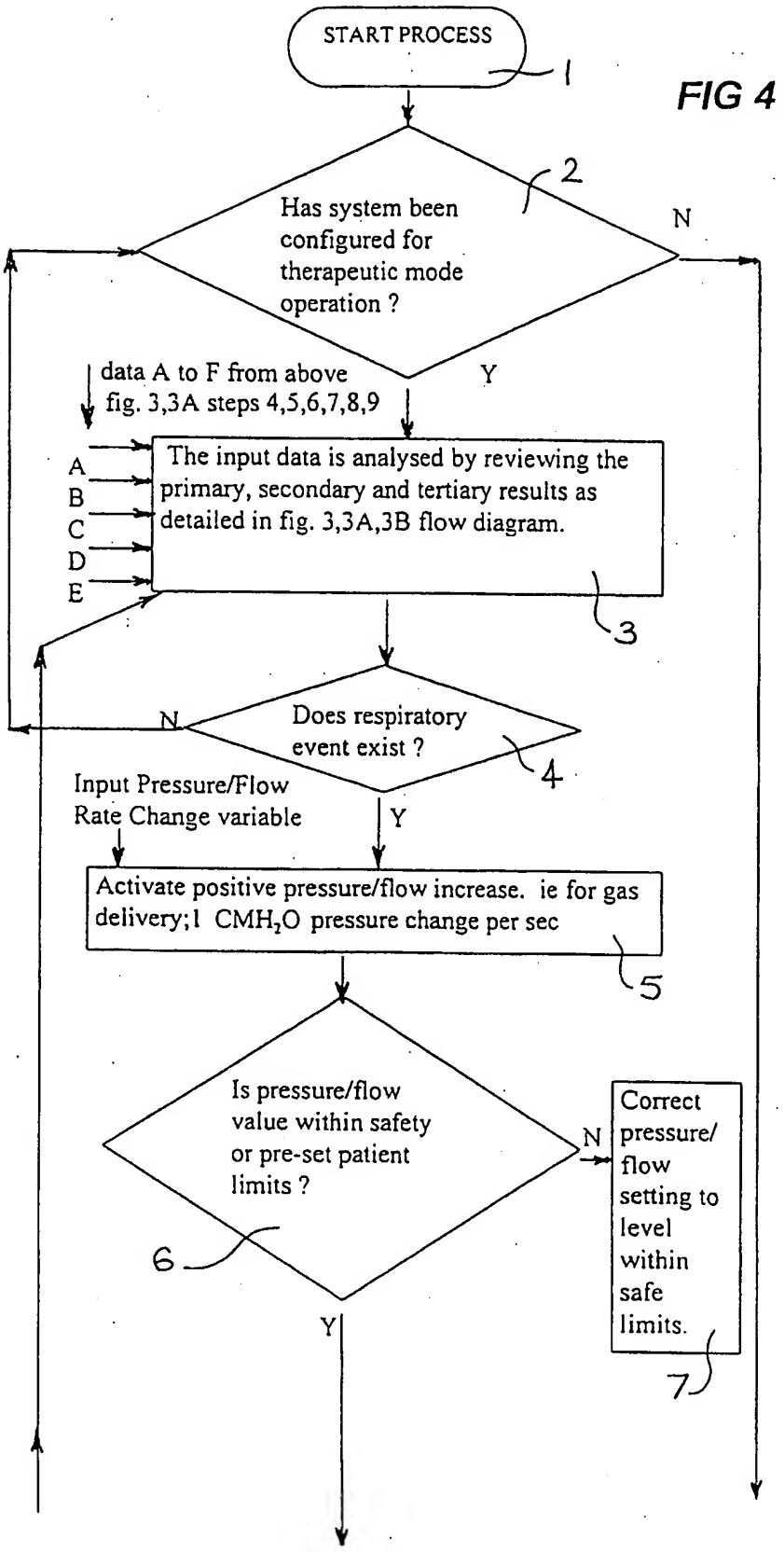
START PROCESS
1
Has system been configured for therapeutic mode operation ?
2
N
Y
data A to F from above fig. 3,3A steps 4,5,6,7,8,9
A
B
C
D
E
The input data is analysed by reviewing the primary, secondary and tertiary results as detailed in fig. 3,3A,3B flow diagram.
3
Does respiratory event exist ?
4
N
Y
Input Pressure/Flow Rate Change variable
Activate positive pressure/flow increase. ie for gas delivery;1 CMH_2O pressure change per sec
5
Is pressure/flow value within safety or pre-set patient limits ?
6
N
Y
Correct pressure/ flow setting to level within safe limits.
7

FIG 4

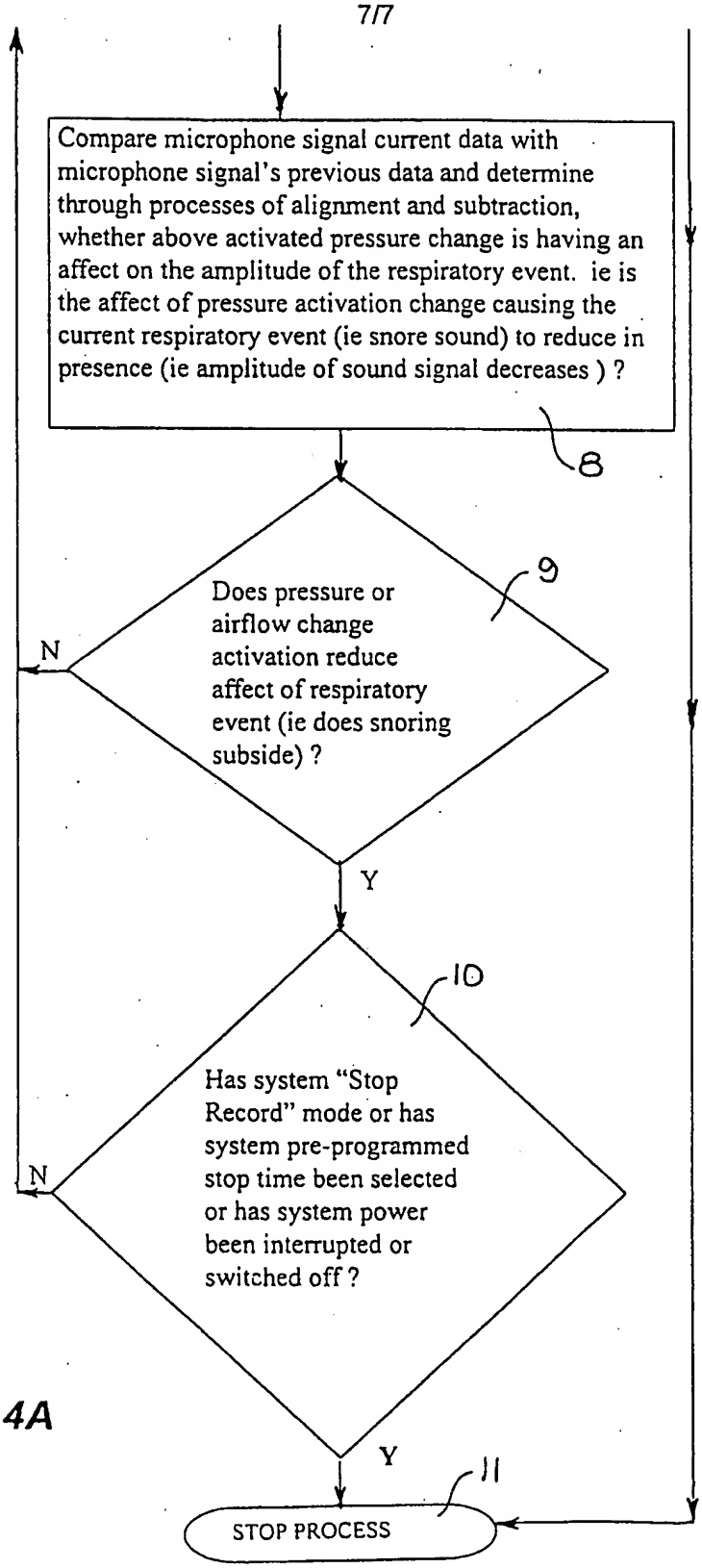
Compare microphone signal current data with microphone signal's previous data and determine through processes of alignment and subtraction, whether above activated pressure change is having an affect on the amplitude of the respiratory event. ie is the affect of pressure activation change causing the current respiratory event (ie snore sound) to reduce in presence (ie amplitude of sound signal decreases) ?
8
Does pressure or airflow change activation reduce affect of respiratory event (ie does snoring subside) ?
9
N
Y
Has system "Stop Record" mode or has system pre-programmed stop time been selected or has system power been interrupted or switched off ?
10
N
Y
STOP PROCESS
11

FIG 4A

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 97/00278

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61M 16/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int Cl : A61B 5/-, A61M 16/-, A62B 7/-, 9/-, G10K 11/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU : A61M 16/00

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT : sleep:, monitor:, diagnos:, respir:, breath:, snor:, wheez:, pressur:,
JAPIO : apn:, hypopn:, sound:, acoustic:, etc

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A, 5199424 (SULLIVAN & LYNCH) 6 April 1993 see abstract, fig 5 see column 6 line 29 - column 7 line 57	1, 2, 8-15, 22, 23, 27-28
X	WO,A, 96/40335 (RESPIRONICS INC) 19 December 1996 see page 11 line 19 - page 12 line 21	1, 2, 8-15, 21, 22, 27-28

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

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Date of the actual completion of the international search
1 July 1997

Date of mailing of the international search report
16 JUL 1997

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 97/00278

C (Continuation) **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A, 94/23780 (RESPIRONICS INC) 27 October 1994 see abstract, fig 1 see page 8 lines 6-25 see page 12 lines 16-34	1, 2, 8-15, 21, 22, 27-28
X	WO,A, 92/22244 (AXE et al) 23 December 1992 see abstract, fig 1 see page 9 line 20 - page 10 line 19	1, 2, 8-15, 21, 22, 27-28
X	US,A, 5551419 (FROEHLICH et al) 3 September 1996 see abstract, fig 1	1, 2, 8-15, 21, 22, 27-28
X	US,A, 5617846 (GRAETZ) 8 April 1997 see abstract, fig 1 see column 1 line 54 - column 2 line 12	1, 2, 8-15, 21, 22, 27-28
X	US,A, 5353788 (MILES) 11 October 1994 see abstract, fig 4 see column 4 lines 55-66	1, 2, 8-15, 21, 22, 27-28
X	WO, A, 93/09834 (UNIVERSITY TECHNOLOGIES INTERNATIONAL INC) 27 May 1993 see abstract, fig 1A see page 5 lines 7-18 see page 10 lines 7-31 see page 15 line 8 - page 16 line 32	1, 2, 8-15, 21, 22, 27-28
X	WO,A, 93/21982 (NEW YORK UNIVERSITY) 11 November 1993 see whole document	1, 2, 8-15, 21, 22, 27-28
X	WO,A, 92/11054 (PURITAN-BENNETT CORP) 9 July 1992 see whole document	1, 2, 8-15, 21, 22, 27-28
X	US,A, 5490502 (RAPOPORT) 13 February 1996 see abstract, column 2 line 38 - column 3 line 50	1, 2, 8-15, 21, 22, 27-28
A	US,A, 5444786 (RAVIV) 22 August 1995	3-7, 23-26

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 97/00278

Box 1 Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1-17, 21-30 are directed to an apparatus and method for controlling the pressure of gas delivered to a patient to prevent deterioration of a monitored respiratory state.

Claims 18-20 are directed to an apparatus for controlling the quantity of a drug to be administered to a patient to prevent deterioration of a monitored respiratory state.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-17, 21-30

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/AU 97/00278

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	5199424	US WO	5245995 8810108	US	5522382	AU	19894/88
WO	9640335	AU US	60474/96 5537997	CA	2196918	EP	777507
WO	9423780	AU US	66296/94 5458137	CA	2159336	EP	699085
WO	9222244	AU US	21892/92 5203343	CA US	2111324 5458137	EP	592492
US	5551419	AU	40463/95	CA	2163855	EP	722747
US	5617846	CA NO	2157815 953455	EP	705615	FI	954092
US	5353788						
WO	9309834	AU	31270/93	EP	612257		
WO	9321982	AU	42405/93	EP	639088	US	5335654
WO	9211054	US EP	5134995 563044	AU US	82154/91 5259373	AU US	40711/95 5549106
US	5490502	AU WO	42405/93 9321982	EP US	639088 5535739	US US	5335654 5546933
US	5444786						

END OF ANNEX

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(71) Applicant *(for all designated States except US)*: ANEO AB [SE/SE]; Maskingatan 3, S-195 60 Märsta (SE).

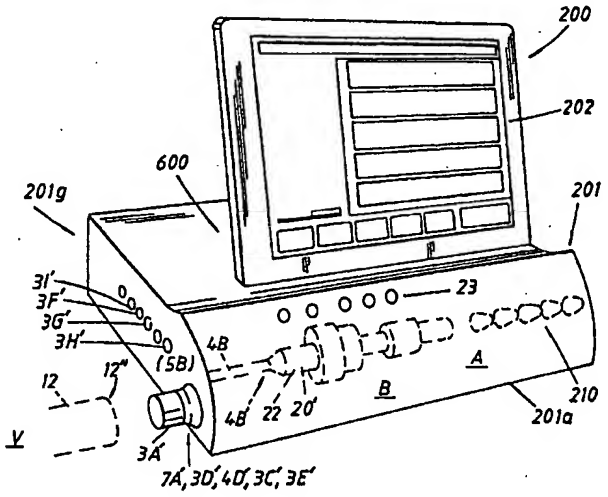
(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: STRÖMBERG, Stefan [SE/SE]; Albods väg 18, S-193 40 Sigtuna (SE).

(74) Agents: ASKERBERG, Fredrik et al.; L.A. Groth & Co. KB, Box 6107, S-102 32 Stockholm (SE).

(81) Designated States: AE, AG, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, DZ, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AN ARRANGEMENT FOR ANAESTHETISING A LIVING CREATURE



(57) Abstract

The invention relates to an arrangement (200) for anaesthetising a living creature (V) and for maintaining said creature in an anaesthetised state, by administering thereto an infused volume of anaesthesia inducing pharmaceutical (22) in liquid phase per unit of time, with the aid of one or more lung ventilator units (A) and one or more infusion units (B). Chosen parts of the lung ventilator unit, with the exception of external insufflation hose, expiration valve, measuring probe and a number of hoses (12), and selected parts of the infusion unit (B), with the exception of cannula (5B) and hose (4B) are mutually combined to form a single equipment unit (201). Some of the parts of the equipment unit are mutually coordinated with respect to communication via a computer unit (600) included in the equipment unit, and the computer unit is adapted to monitor unit related criteria and creature related criteria.

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AN ARRANGEMENT FOR ANAESTHETISING A LIVING CREATURE

Field of invention

The present invention relates to an arrangement for initially anaesthetising a living creature and to keep the creature within adapted levels of said anaesthetic state, the so-called depth of anaesthesia.

Such states and depths of anaesthesia are achieved by infusing or injecting into a living creature a volume of anaesthesia inducing pharmaceutical in a liquid phase per unit of time.

By "infused" is meant the continuous or intermittent and/or controllable delivery of said pharmaceutical (anaesthetic) to a blood-carrying vessel, preferably intravenously.

During this state there is required, among other things, the use of a lung ventilator and associated control unit, and an infusion unit and associated control unit, to regulate the increase in or reduction in the volume of pharmaceutical per unit of time required to regulate the depth of anaesthesia.

In addition, arrangements of this kind comprise and/or include a plurality of sensors and/or measuring probes adapted to sense selected creature-associated criteria and to produce a signal that corresponds to the chosen criterion and its value or intensity at that moment in time.

Examples of criteria thus selected and their intensity will be mentioned in the following text.

The invention can be applied to any living creature that has a lung function and will be illustrated in the following with reference to its application on a human being, represented by a patient undergoing surgery, by way of simplification.

Description of the background art

With respect to earlier known apparatus and arrangements for anaesthetising a patient to a chosen depth of anaesthesia, it is normal to divide such states into three different categories, depending on the degree of consciousness of the patient, namely:

- general anaesthesia, a state in which the patient is rendered unconscious artificially and kept within adapted degrees or levels of unconsciousness (depth of anaesthesia);
- regional anaesthesia, a state of insensitivity in the spine of a patient; and
- local anaesthesia a state which is mainly applicable to minor surgery or treatment.

The patients are conscious in the latter two categories.

The present invention is adapted for application in the general anaesthesia category.

This category includes two different groups of anaesthesia, namely inhalation anaesthesia and total intravenous anaesthesia.

There is used within the first anaesthesia group, inhalation anaesthesia, a lung ventilator that includes vaporiser equipment for anaesthesia inducing pharmaceutical, said lung ventilator creating conditions for the insufflation and expiration of air or air mixed with gaseous oxygen, which is mixed, in turn with anaesthesia inducing gases.

Although apparatus designed for inhalation anaesthesia have found wide use, they require the appropriation of very complicated equipment, partly to enable the insufflation and expiration phases to be controlled and partly to administer the supply of gaseous pharmaceutical, and also to evaluate patient related criteria and to regulate said criteria when necessary.

Thus, it is likely that anaesthesia inducing gases will accompany the expiration gas in each expiration phase and consequently it is necessary to remove these gases from every enclosed space, such as the operating theatre, effectively and at short intervals. In addition, the equipment must, of course, be gas tight in general.

It is also known in the case of such practice to assemble an inhalation anaesthesia related system within respective clinics with the aid of different apparatus obtained from different manufacturers and designed for different purposes.

It is also known to appropriate a single system from a single manufacturer. Such systems, however, are highly complicated and the component parts of such systems make the equipment extremely heavy. It is also found that such a system

is space consuming and expensive and that the necessary inspections for possible leakage are very difficult to carry out.

The present invention relates to and includes an arrangement within the second anaesthesia group, i.e. total intravenous anaesthesia, wherein a volume of occurring or existing anaesthesia-inducing pharmaceutical in liquid phase is allowed to infuse per unit of time into the bloodstream of the living creature or patient.

It is necessary in this case to use a lung ventilator and an infusion unit which, with the aid of a control unit, is able to induce a given depth of anaesthesia in the patient and to keep the patient within adapted levels of said chosen depth of anaesthesia.

It is known in this respect to use a number of apparatus taken from different manufacturers and to assemble these apparatus into a system or an arrangement. In order to induce a given depth of anaesthesia in a patient, each such system requires the use of a number of apparatus and measuring devices which function to enable a number of important patient criteria to be evaluated and to enable the well-being of the patient to be controlled. These criteria have normally been presented as instantaneous values and/or curves on the display surface of each apparatus.

Criteria that concern the well-keeping/treatment of a patient are designated therapeutic criteria and are detected/sensed, regulated and evaluated in one or more therapeutic units.

Criteria that relate to patient diagnosis or patient supervision are referred to as diagnostic criteria and are sensed/detected and evaluated in one or more diagnostic units.

Some significant units and criteria in the present context have been listed in Figure 1, in which reference sign A identifies a lung ventilator and an associated control unit; B identifies an infusion unit and associated control unit for making necessary adjustments to the volume of anaesthesia inducing pharmaceutical per unit of time; C identifies a unit which senses/detects prevailing air pressure, i.e. the air pressure in the mouth of the patient; D identifies a unit which evaluates the flow of air into the patient's lungs and, when necessary, also out of the lungs; E

identifies a unit which evaluates the CO_2-content and the O_2-content of the air entering the lungs, and when necessary also the expiration air; F identifies a unit for evaluating ECG-values; G identifies a unit that evaluates blood pressure values NIBP; H identifies a unit for establishing oxygen saturation in the blood (SpO_2); I identifies a unit which evaluates the degree of consciousness of the patient (the depth of anaesthesia) via sensed brain activity (the BIS-values); and J identifies a unit which evaluates PEEP-value.

It is known in systems of this nature adapted for total intravenous anaesthesia to allow a number of the criteria given under A-J above to be interconnected and combined in a common unit.

For instance, it is known to combine the units for criteria C and J and for A, D and E respectively into a single unit. The criterion B and combinations of criteria F, G and H normally require separately operated and individual units.

Known technology teaches the use of the infusion unit B and the lung ventilator A as separate units. These units are used to control the well-being of the patient and therefore include a number of therapeutic units.

Other equipment and units are primarily designed to produce instantaneous values or curves for other relevant patient-related criteria and include a number of diagnostic units.

By instantaneous values shall be understood measured values that can be evaluated instantaneously in the true meaning of the word, and also the formation of mean values of a selected number of sensed/detected instantaneous measurement values.

In the case of so-called multi-parameter monitors, it is known to co-ordinate the evaluated instantaneous values and the values for presentation of time-related graphs for selected relevant criteria and to show these graphs on a display surface.

Summary of the present invention

Technical problems

When taking into consideration the technical deliberations that a person skilled in this particular art must make in order to provide a solution to one or more

technical problems that he/she encounters, it will be seen that on the one hand it is necessary to realise the measures and/or the sequence of measures that must be undertaken to this end, and on the other to realise which means is/are required in solving one or more of said problems. On this basis, it will be evident that the technical problems listed below are highly relevant to the development of the present invention.

When considering the present standpoint of techniques as described above, it will be seen that a technical problem is one of providing with simple means an arrangement which enables the infusion of anaesthesia inducing pharmaceutical and which is based on principles for total intravenous anaesthesia while using one or more lung ventilator units and one or more infusion units, with first means for monitoring unit-related criteria, and second means for monitoring patient-related criteria, therewith creating conditions for a compact and mobile arrangement.

In this respect, a technical problem resides in realising the significance of and the advantages afforded by allowing the component parts of the chosen lung ventilator, with the exception of insufflation hose, expiration valve, measuring probe and a number of hoses, and the component parts of the infusion unit, with the exception of cannula and hose, to be combined into a single equipment unit, and to mutually co-ordinate certain of said equipment unit parts from the aspect of communication through the medium of a computer unit arranged in the equipment unit, and to program the computer unit to monitor patient related criteria and unit related criteria.

In addition, a technical problem resides in realising the significance of and the advantages that are associated with programming the computer unit to distinguish between therapeutic criteria and diagnostic criteria through the medium of therapeutic units and diagnostic units included and mounted in said equipment unit.

Another technical problem resides in realising the significance of and advantages afforded by structuring one or more therapeutic unit and/or one or more diagnostic units on a printed circuit board or card and, when applicable, function units mounted on or related to said circuit board, and co-ordinating several such

boards in the equipment unit, wherewith an input of respective units is coupled internally in the equipment unit to one part of a two-part coupling means, where said parts are fastened to and co-ordinate in said equipment unit, and to realise that said parts of the coupling means belonging to said equipment unit shall be comprised of one or more hose couplings and one or more couplings/connections for electric conductors or cables.

It will also be seen that a technical problem resides in the provision of conditions with the aid of simple measures that enable an external insufflation-hose section for the lung ventilator unit and its coupling part associated with said equipment unit to be co-ordinated with further external hose parts so as to enable an external hose bundle or assembly to be used, said hose bundle conveniently including a hose for controlling a patient-proximal expiration valve, two hose parts for measuring pressure differences, a hose part for measuring pressure and/or a gas sampling hose part.

In addition, a technical problem resides in providing with the aid of simple measures conditions which allow the infusion unit to include a container that is held detachably by the equipment unit and that contains an anaesthesia inducing pharmaceutical in liquid phase.

Another technical problem is one of creating with the aid of simple measures conditions which enable the coupling parts associated with the equipment unit to be connected to a measuring probe, sensor or like device peripherally situated and separated from the equipment unit, through the medium of a hose part or an electric conductor, where said measuring probe, sensor or like device may include electronic circuits that are designed to sense the occurrence of patient related criteria and to establish the values of said criteria.

It will also be seen that a technical problem resides in providing with the aid of simple measures conditions that will enable such an equipment unit to be coupled to and/or readily releasably connected to a display unit adapted to display on a display surface one or more of the instantaneous values of criteria and/or timewise variation of said criterion.

In this respect, a technical problem resides in realising the significance of and the advantages that are afforded by presenting requisite diagnostic criteria

and requisite therapeutic criteria in a co-ordinated fashion, thereby greatly assisting the anaesthetist and the surgeon in controlling and regulating the therapeutic criteria and/or diagnostic criteria of the patient, such as the depth of anaesthesia and/or other changeable states.

Another technical problem is one of creating with the aid of simple means or measures conditions which enable the timewise variation of a number of chosen criteria to be presented on an image screen or display surface with at least some chosen time axes co-ordinated, for instance superimposed with respect to each other, and, when necessary, compensating for any lag time in evaluating the measuring result.

Another technical problem is one of providing with the aid of simple measures conditions that allow the timewise variation of one or more, although only a few, chosen criteria to be presented on an image screen or display surface in a time-axes time scale that is different to the time axes for other criteria.

Another technical problem is one of realising the co-ordination that is required to allow the predominant part of requisite circuits, units and equipment to be combined into a single equipment unit, where requisite measuring points, measuring probes, sensors, etc. can be connected to said equipment unit via coupling means in an easy and functionally reliable fashion.

Another technical problem resides in providing an arrangement capable of readily effecting in the equipment unit such requisite processes as gas sampling/measuring, flow measuring, volume measuring, pressure measuring, ECG-measuring, saturation measuring and/or measuring the depth of anaesthesia.

Yet another technical problem is one of providing an arrangement of the kind described in the introduction in which the equipment unit used is adapted to include the major part of a lung ventilator and its associated control unit, and to couple said ventilator to a computer unit.

It will also be seen that a technical problem is one of realising the significance of providing an arrangement in which the entire lung ventilator is incorporated in the equipment unit, with the exception of a hose portion that conducts insufflation gas to the patient, an outer portion of said hose for connection to an expiration valve, one or more hose portions extending between said valve and said

unit, a hose portion for actuation of the expiration valve to one of two positions from the equipment unit, a hose portion for determining gas pressure values and an adapted lowest overpressure value, and two hose portions belonging to the measuring probe for transferring flow-dependent gas pressure values to the equipment unit, said values being used to measure flow, and also said measuring probe and a hose portion for gas analysis.

It will also be seen that a technical problem resides in creating conditions which enable all important function units to be combined in one single equipment unit, so that said unit can be attached to a readily accessible first part of a two-part hose coupling, said coupling part being adapted for coaction with a number of further hoses in addition to coaction with an outer hose part for insufflation gas.

It will also be seen that in respect of an arrangement of the kind described in the introduction a technical problem resides in enabling readily available first coupling parts of one or more two-part hose couplings to be connected to the equipment unit, where said first coupling parts are adapted for coaction with one or more hoses for evaluating different selected criteria, such as CO_2-content, O_2-content, breathing frequency and like alternatives for pressure actuation of an expiration valve.

Similarly, it will be seen in respect of an arrangement of the kind described in the introduction that a technical problem resides in enabling one or more first coupling parts of one or more readily accessible two-part electric coupling parts to be attached to said equipment unit, where said first coupling parts are adapted for coaction with one or more external electric cables which carry electric signals representative of different chosen criteria, such as the timewise presentation of ECG-values, PLET-values and BIS-values, and instantaneous values of the same or different chosen criteria, such as the HR-value, S_pO_2-value and BIS-value respectively.

Another technical problem resides in enabling the use of a display unit that is designed for inclusion in an arrangement and which co-acts with an equipment unit for presenting thereon timewise variations of the measurement values applicable to chosen criteria and the instantaneous values of the same or other chosen criteria, and structure these values on said display surface so that they

can be readily discerned and read, said display surface presenting one or more patient related criteria during a chosen depth of anaesthesia caused by said patient infusing a volume of anaesthesia inducing pharmaceutical per unit of time.

It will also be seen that a technical problem resides in enabling the measurement values and data obtained from chosen patient related criteria to be distributed so that said values and data can be read easily on the display surface and readily modified, for instance through the medium of display-surface related fields and the orientation of said fields and/or through the medium of button or knob actuation.

Another technical problem is one of realising the significance of allowing a first wide surface area of the display surface to be adapted to show the timewise variation of a number of criteria, and a second smaller surface area adapted to show the instantaneous values, the highest and lowest values etc. of a number of criteria.

It will also be seen that a technical problem is one of realising the significance of and the advantages afforded by allowing the first surface area to be adapted to show the timewise variation of a number of criteria, by orientating a chosen number of said criteria with the time axes being mutually equal and in superimposed relationship.

A further technical problem is one of realising the significance of and the advantages afforded by allowing a second surface area to be divided into fields such that relevant criteria can be displayed in each field, for instance in an abbreviated form, and to display adjacent thereto the instantaneous value of the criteria and the alternative maximum and minimum values or calculated values thereof.

In respect of an arrangement of the kind described in the introduction and comprising an equipment unit and a display unit, still another technical problem is one of realising the advantages that are afforded when said display unit is rotatably mounted on and easily detached from the front part of the equipment unit, such as above a container that encloses anaesthesia inducing pharmaceutical and that can be actuated by the control unit of an infusion unit, and also to realise the significance of such placement.

It will also be seen that a technical problem is one of creating with the aid of simple measures conditions that enable a control circuit in the control unit for regulating the volume of anaesthesia inducing pharmaceutical supplied by unit of time to be actuated through the medium of actuating means positioned adjacent to and preferably above said container.

Another technical problem is one of realising the significance of and the advantages afforded by allowing one or more control circuits in said control unit in the control unit for regulating criteria related to the lung ventilator to be actuated through the medium of actuating means located adjacent to and on one side of said container.

Another technical problem is one of realising the significance of and the advantages afforded by allowing one or more control circuits for controlled regulation of other criteria to be actuated through the medium of actuating means positioned in one or more rows within a third surface area of a display surface.

Another technical problem resides in creating conditions for providing within the limited volume of the equipment unit activatable regulating devices that are adapted to hold a chosen value of a chosen criterion constant for regulating purposes.

In addition to these problems it will be seen that a further technical problem resides in creating with the aid of simple measures an arrangement for total intravenous anaesthesia, where said arrangement can be managed much more simply than earlier known combined and co-ordinated arrangement set-ups and which is designed to fulfil requirements laid down by the authorities, which results in reduced maintenance costs, which is more reliable in operation, and which satisfies the desire for less or small bulk, and which is therewith mobile.

Another technical problem is one of realising the significance of and the advantages afforded by enabling the expiration gas of the patient to be conducted out into the room while the patient is anaesthetised, therewith facilitating cleaning of the ventilator and reducing the wear and tear thereon, while utilising a much smaller compressible volume (less than half).

The use of a display unit enables different magnitudes to be combined on the display surface and to phase shift and time-adapt the magnitudes, such as a pressure curve against a sample CO_2-curve.

It is also possible to plot one magnitude against another, for instance in an XY-diagram (PQ-loops and PV-loops).

It is also possible to establish co-variations, for instance changes in blood pressure or BIS in respect of a changed infusion rate, via a TREND-function.

A further technical problem resides in the creation of conditions with the aid of simple measures and with the use of a computer unit which enable advanced calculations or computations to be carried out by collecting together all parameters, for instance lung mechanics and indirect calorimetry and other associated advanced expert systems, where the computer is able to monitor a plurality of parameters and to draw logical conclusions therefrom, for instance give an early indication of problems and/or initiate the need for advice, for instance in reducing lung compliance (the stretchability of the lung).

Another technical problem resides in creating with the aid of simple measures and with the use of a computer unit conditions that make possible a closed-loop anaesthesia process, e.g. enable the infusion rate from which the BIS-values are obtained to be controlled, or to control the lung ventilator on the basis of the CO_2-values obtained.

Another technical problem is one of creating with the aid of simple measures and with the use of a computer unit conditions for reducing and/or totally eliminating mischievous alarms (several alarms resulting from the same basic cause) and to make possible so-called smart alarms, wherewith the computer unit initially sets the alarm limits on the basis of obtained patient criteria, therewith making things easier for the user.

Another technical problem is one of creating with the aid of simple measures and with the use of a computer unit conditions which enable a display image or display surface to be transmitted to another locality via telecommunications, e.g. via the Internet.

This enables the display surface to be presented on-line for consultation with another doctor in another district and locality.

The invention also provides the option of presenting display images of differing advanced degrees and therewith adapt the system to the needs and experience of the user.

The interface can also be readily updated for different languages and/or to provide technical services and updating of software in the system over the telecommunications network.

A technical problem resides in creating with the aid of simple measures and with the use of a PC-compatible computer unit conditions for advanced statistic data processing, and economic follow-up of the use of the machine and the consumption of pharmaceuticals for instance, and enables the use of standard PC-components, for instance card readers, for entering patient journals, and to utilise readily the speed and inexpensive development of PC-technology in other respects.

A further technical problem is one of creating with the aid of simple measures and with the use of a computer unit conditions for plotting the infusion characteristic of the infusion unit on the display surface and also to allow the user to insert the value mg/kg/h instead of ml/h.

Solution

The present invention thus takes at its starting point an arrangement for anaesthetising a living creature by administering thereto an infused volume of an anaesthesia inducing pharmaceutical in liquid phase per unit of time, while using one or more lung ventilator units and one or more infusion units, and by using first means to monitor unit-related criteria and second means to monitor patient related criteria.

With the intention of solving one or more of the aforesaid technical problems it is proposed in accordance with the invention that selected parts of the lung ventilator unit, with the exception of insufflation hose, expiration valve, measuring probe and a number of hoses, and selected parts of the infusion unit, with the exception of cannula and hose, are combined to form a single equipment unit, that certain of said equipment unit parts are mutually co-ordinated with respect to

communication via a computer unit included in the equipment unit, and that said computer unit is adapted to monitor unit-related criteria and patient-related criteria.

According to proposed embodiments that lie within the scope of the present invention it is proposed that the computer unit is adapted to distinguish between therapeutic criteria and diagnostic criteria through the medium of therapeutic units and diagnostic units included in the equipment unit.

It is also proposed that one or more therapeutic units and/or one or more diagnostic units are structured on a printed circuit board or card and that, when applicable, function units are mounted on said board, and also that a plurality of such boards are co-ordinated in the equipment unit, and that an input of respective units is coupled internally of the equipment unit to one part of a two-part coupling device where said parts are attached to and co-ordinated in the equipment unit .

The coupling parts belonging to the equipment unit are comprised of one or more hose couplings and one or more electric connectors.

It is also proposed that an external hose part coupled to the lung ventilator unit and that a number of other external hose parts are arranged in a hose bundle or hose assembly that includes a hose part for insufflation gas, a hose part for controlling a patient-proximal expiration valve, two hose parts for measuring pressure difference, a pressure measuring hose part and/or a gas sampling hose part.

It is also proposed that the infusion unit will include a container or vessel that can be held firmly to the equipment unit but readily removed therefrom, said container containing an anaesthesia inducing pharmaceutical in liquid phase.

It is also proposed that the coupling parts of the equipment unit shall be connectable to a measuring probe, sensor or the like separate from the equipment unit, through the medium of an external hose part or an external electric conductor, wherewith said measuring probe, sensor or the like may include electronic circuits adapted for sensing/detecting the presence and the value of patient related criteria.

It is particularly proposed that a display unit is coupled to and/or secured to said equipment unit, and that said display unit is adapted to show the instanta-

neous values of one or more criteria and/or the timewise variation of said criteria on a display surface.

With the intention of solving one or more of the aforesaid technical problems it is also proposed in accordance with the invention that one or more first criteria related to one or more diagnostic units, and that one or more second criteria related to one or more therapeutic units can be presented on the display surface of a display unit, that one or more of said first criteria is/are chosen for display on the display surface as instantaneous values, and that one or more of said first criteria is/are chosen for display on said display surface as the timewise variation of the criterion.

By way of proposed embodiments that lie within the scope of the present invention it is also suggested that one or more of said second criteria is/are selected for display on the display surface as instantaneous values, and that one or more of said second criteria is/are selected for display on said display surface as timewise variation of the criterion.

In the case of certain criteria that are selected for display as the timewise variation of the criterion, the time axes are co-ordinated and disposed in superimposed relationship.

It is necessary for sensor associated signals to be delayed in respect of some criteria.

It is also proposed that the instantaneous values of one or more criteria related to one or more diagnostic units and/or the instantaneous values of one or more criteria related to one or more therapeutical units can be stored in the memory of the computer and presented as timewise variations of the criterion, as required.

It is also proposed that a few selected instantaneous values are stored in the memory time-related for presented time curves, so that the trend taken by the curve or certain variations in a time compressed form can be repeated.

It is also proposed in accordance with the present invention that an equipment unit will include a lung ventilator and its associated control unit, and an infusion unit and its associated control unit, and that said equipment unit is also adapted to include and detachably hold a container or vessel that encloses an an-

aesthesia inducing pharmaceutical in liquid phase, and that said equipment unit is also adapted to include or to co-act with said display unit.

It is also proposed that a first coupling part of a two-part hose coupling is attached to the equipment unit, and then particularly to one end-wall part thereof, said coupling part being adapted for coaction with a hose part that functions to conduct a gas flow generated in the ventilator and intended for insufflation.

It is also proposed that one or more first coupling parts or one or more two-part hose couplings is/are attached to the equipment unit, and then particularly to one end-wall part thereof, said coupling part being adapted for coaction with one or more hoses for measuring pressure, measuring flow and/or analyzing gas, wherewith the equipment unit is associated with means for evaluating different criteria, such as CO_2-content, O_2-content, breathing frequency and similar criteria.

It is also proposed that one or more first coupling parts of one or more two-part electric connectors is/are connected to the equipment unit, particularly to one end-wall part thereof, wherein said connector parts are adapted for coaction with one or more external electric cables that carry sensor-related electric signals representative of different criteria, such as ECG-values, SpO_2-values, BIS-values, PLET-values.

It is also proposed in accordance with the invention that there is included a display unit whose display surface is divided so that there can be presented on one section of said surface one or more criteria relating to an anaesthetised patient, where the anaesthetised state of said patient has been caused by infusion of a volume of anaesthesia inducing pharmaceutical per unit of time, wherein it is particularly proposed in accordance with the invention that a first surface area of said display surface shall be adapted to display the timewise variation of a number of criteria, and that a second surface area of said display surface shall be adapted to display the instantaneous values of a number of criteria.

It is also proposed in accordance with the invention that a first surface area of said display unit shall be adapted to display the timewise variation of a number of criteria by arranging at least some of the time axes equally and in superimposed relationship.

In addition, it is proposed that a second surface area shall be divided into fields and that one or more criterion, suitably in an abbreviated form, and the instantaneous value of respective criterion can be displayed within each field.

In the case of an arrangement that includes an equipment unit and a display unit it is proposed that the display unit is rotatably mounted on and readily removable from the front part of the equipment unit, above a container that encloses anaesthesia inducing pharmaceutical and that is activatable by the control unit of the infusion unit.

It is also proposed that the control unit will include a control circuit for regulating the volume of anaesthesia inducing pharmaceutical administered per unit of time that can be activated by activating means, preferably positioned adjacent to and above said container.

It is also proposed that control circuits in the control unit for regulating criteria related to the lung ventilator can be actuated via activating means, preferably positioned adjacent to and on one side of said container.

Control circuits in a control unit for regulating a number of criteria can also be actuated via activating means that are preferably orientated in row within a third surface area of said display.

It is also proposed that the equipment will include activatable control means adapted to hold a value of a selected criterion constant.

Advantages

Those advantages primarily afforded by an arrangement for anaesthetising a living creature or patient by administering to the patient an infused volume of anaesthesia inducing pharmaceutical in liquid phase per unit of time, and while using, inter alia, a lung ventilator and an infusion unit together with associated control units, reside in the creation of conditions which enable the requisite circuits to be combined into a single equipment unit that can be easily transported and that requires little space, wherewith the requisite sensors, measuring probes, etc. to be coupled to the equipment unit can be connected readily and positively between patient and equipment unit.

The invention also includes a display unit which provides conditions for monitoring all relevant criteria in a total intravenous anaesthesia-induced state in a simple and safe fashion, so that established relative criteria and their timewise variation or instantaneous values can be overseen during surgery.

It is also possible with the aid of computer associated circuits to create conditions in which the evaluated measurement values are delayed so as to co-ordinate their appearance with respect to time.

The criteria-related measurement values can be held constant (closed loop) via computer related circuits, expert systems can be co-ordinated over telecommunications networks, and conditions can be created for distance use, relevant alarm functions can be co-ordinated, and different alarm criteria can be given different priorities.

The primary characteristic features of an inventive arrangement, in accordance with the present invention, are set forth in the characterizing clause of the accompanying claim 1.

The primary characteristic features of a display unit according to the present invention are set forth in the characterizing clause of the accompanying claim 21.

Brief description of the drawings

An earlier known arrangement and two inventive arrangements for anaesthetising a living creature or patient by administering thereto an infused volume of anaesthesia inducing pharmaceutical in liquid phase per unit of time will now be described in more detail with reference to the accompanying drawings, in which

Figure 1 lists a number of known unit-related and patient-related criteria that can be utilised and/or evaluated beneficially with the patient in an anaesthetised state, through the medium of one or more therapeutic units and one or more diagnostic units;

Figure 2 is a perspective view of an earlier known system in which various therapeutic units and various diagnostic units are disposed in a room in mutually spaced relationship;

Figure 3 is a block diagram illustrating a first embodiment of an integrated equipment unit according to the invention;

Figure 4 is a perspective external view of an equipment unit and associated display unit included in the inventive arrangement;

Figure 5 is a plan view of the display surface of a display unit and shows proposed orientation of first, second, third and fourth surface areas such that timewise variation of criteria and a number of instantaneous values of said criteria can be monitored graphically and in a time relationship;

Figure 6 illustrated the principle connection of a measuring probe and a valve for enabling the flow and volume of insufflation gas and expiration gas to be determined and controlled, and also other criteria related to said gas;

Figure 7 illustrates an example of a hose bundle with a hose cross-section that can be used as an integrated connection between the equipment unit and the valve/measuring probe shown in Figure 6; and

Figure 8 is a block diagram of a second integrated equipment unit according to the invention, including a number of electric circuits, a lung ventilator and associated control unit, and an infusion unit and associated control unit for regulating the supply of anaesthesia inducing pharmaceutical, and a computer unit and connected display unit.

Description of known embodiments

Figure 1 lists a number of pieces of equipment, units and electric/electronic circuits required to anaesthetise a living creature or a patient by administering an infused volume of anaesthesia inducing pharmaceutical per unit of time and keeping the patient anaesthetised during surgery, and thereafter to arouse the patient from said anaesthetised state.

Figure 1 is intended to illustrate a number of therapeutic units adapted to control the well-being of the patient, and a number of diagnostic units adapted to sense/detect and evaluate patient-related criteria for visually and/or audibly in-

forming the anaesthetist and/or surgeon as to the state of the patient, and to provide the possibility of regulating current values for each chosen criterion.

Thus, the reference A in Figure 1 identifies a lung ventilator. Lung ventilators of this particular kind are complicated and are known to the art and, in the following text, are simplified to comprise principally a drive unit 1A and a control unit 2A.

The lung ventilator A includes a first hose 3A adapted for delivery of insufflation gas to a patient V, and an insufflation valve 5A which is connected to the ventilator A by the hose 3A.

The lung ventilator A also includes a second hose 4A for expiration of gas from the patient V, and an expiration valve 6A connected to the hose 4A, said second hose 4A having the same cross-section as the hose 3A.

The mutually opposite ends of the hoses 3A and 4A are combined in a patient-adapted mouthpiece.

The reference B identifies a schematically illustrated and known infusion unit, where movement of an infusion syringe is effected by a part 1B and a control unit 2B.

A unit B of this kind is known to the art and is based on a container in the form of a syringe 3B that encloses an anaesthesia inducing pharmaceutical in liquid phase, and which an actuator means of a stepping motor functions to press a plunger into the syringe, wherewith pharmaceutical can pass through a hose 4B so as to create infusion of pharmaceutical into the patient's bloodstream. The control circuit 2B is designed to increase or decrease the volume infused per unit of time in a regulating fashion.

The distal end of the hose 4B is connected to a cannula 5B inserted in the patient's bloodstream.

C identifies a unit which senses the air pressure prevailing in the mouth and lungs of the patient, and includes an actuator part 1C and a control unit 2C. The instantaneous pressure in the mouth or oral cavity of the patient can be detected and determined through the medium of a hose 3C connected to the patient's mouth. This also enables the PEEP-pressure (J) to be evaluated, this pressure denoting the air pressure between insufflation phases.

D identifies a unit which includes a sensing unit 1D and a control unit 2D and which functions to evaluate the flow of gas (air) into the patient's lungs and, when necessary, the flow of expiration gas.

The unit 1D is connected to a sensor or measuring probe 5D by means of two hoses 3D and 4D, and the sensor or measuring probe 5D is designed to initiate measurement of the flow, through the medium of pressure differences P1 and P2 in the hoses 3D and 4D. As a result of time-related integration in the control unit 2D, the sensor or measuring probe is also able to establish the volume during an insufflation and expiration phase respectively in addition to establishing said flow.

The measuring probe 5D may be of the kind described and illustrated in more detail i US Patent Publication 5 088 332.

The reference letter E in Figure 1 identifies a unit which establishes the CO_2-content and O_2-content of the insufflation gas and/or the expiration gas, said unit including a sensing/detecting unit 1E and an evaluating unit 2E. A hose 3E is connected to the unit 1E. The evaluating unit 2E includes circuits that enable the instantaneous value of the CO_2-content and/or the O_2-content to be established and/or the timewise variation in the pulsating insufflation or expiration gas.

F identifies a unit for establishing the patient's ECG-values and for evaluating the timewise variation of these values with the aid of a sensing unit 1F and an evaluating unit 2F.

One or more measuring points or pads are applied to the patient and connected by an electric conductor 3F, wherewith electric signals are detected and evaluated partially in the unit 1F.

G identifies a blood pressure evaluating unit that includes a sensing unit 1G and an evaluating unit 2G. More particularly, the unit evaluates an NIBP-value (Non Invasive Blood Pressure), by observing pressure variations in the hose 3G.

H identifies a unit that evaluates blood oxygen saturation, in which significant electric signals carried on a conductor 3H are received in a sensing unit 1H and evaluated in an evaluating unit 2H. This value is designated SpO_2. The same unit can be also used to evaluate a PLET-value.

The letter I identifies the process of evaluating the degree of consciousness or the depth of anaesthesia of a patient through the medium of a unit that includes a receiver circuit 1I and a control circuit 2I and which functions to evaluate the instantaneous brain activity of a patient.

Electric signals representing the instantaneous brain activity of the patient arrive on the conductor 3I and are received in a circuit 1I and processed in the evaluating unit 2I so as to be able to show timewise variation of the degree of consciousness and therewith enable the depth of anaesthesia of the patient to be evaluated.

The letter J identifies a device for establishing the lowest air value in respect of lung overpressure. This value can be determined under C.

Figure 2 is a perspective view of an earlier known array of apparatus for achieving total intravenous anaesthesia, where the individual apparatus or pieces of equipment have been combined and placed in an operating theatre in a co-ordinated manner.

Figure 2 shows only some of the units and criteria shown in Figure 1, these units and criteria having been given the same reference signs for the sake of illustration.

Each of the aforesaid evaluating units is designed to generate and alarm when the evaluated measurement value falls below or exceeds a predetermined limit of value.

Description of embodiments at present preferred

Figure 3 is a block diagram illustrating schematically an arrangement 200 constructed and integrated in accordance with the principles of the invention, said arrangement including an equipment unit 201 (shown more clearly in Figure 4) which comprises mutually connected necessary pieces of equipment such as to create a mobile unit to which there is connected a display unit 202 having a display surface according to Figure 5.

The timewise variations of the values and the criteria to be evaluated and presented on the display surface 202' of the display unit 202 are in accordance with the criteria shown in Figures 3, 4 and 5 (within parenthesis);

(F) the timewise variation of ECG-values;

(E) the timewise variation of the CO_2-values (or possibly the O_2-values);

(H) the timewise variation of the PLET-values with respect to pulsation and strength of heart beats;

(C) the timewise variation of the air path pressure P (or the flow rate Q); and

(I) the timewise variation of the depth of anaesthesia (BIS) of the patient.

The time axes wander from left to right for all criteria.

A time axis of 20 seconds is proposed in the illustrated case. On the other hand, a time axis of about 2 hours is chosen for the BIS-curve.

The time axis of the BIS-curve can be changed so as to compress the time axis in respect of times that are longer than the maximum given time of 2 hours, so that all measurement values will be visible during the entire operation (surgical).

With the respect to the values and criteria of instantaneous values, the display surface 202' of the display unit 202 in Figure 5 shall be divided so as to enable the following values to be determined from said criterion (in parenthesis):

(G) the NIBP-value (mmHG) with respect to the systolic blood pressure, a mean value and the diastolic blood pressure;

(F) the HR-value (BPM) denotes the heart frequency;

(E) the $EtCO_2$-value denotes the CO_2-value in percentage at the end of each expiration phase;

(E) the RR-value (BPM) denotes the breathing frequency calculated from the $EtCO_2$-value;

(H) the SpO_2-value denotes in percentage the blood oxygen saturation value;

(E) the FiO_2-value denotes the fraction of inspired oxygen content in the insufflation gas and possibly also in the expiration gas (FeO_2) ;

(D) the VL-value (litres) denotes the volume of insufflated gas and the volume of expired gas;

(C) the P-value (cm H_2O) denotes the pressure of the respiratory tract and PEEP-value (J), disclosing the pressure between two insufflation phases;

(B) the V-inf. value (ml) denotes the volume of anaesthesia inducing pharmaceutical delivered to the patient;

(B) the P occl-value denotes the pressure in the container for the infusion unit, in the form of a bar graph; and

(I) the BIS-value denotes the depth of anaesthesia or the degree of consciousness of the patient in percent.

In the case of the present application it is necessary to force insufflation gas periodically to the patient V through an insufflation hose 3A, whereas expiration gas is allowed to pass directly to the surroundings. This can be effected through the medium of a pressure-actuated valve 15. It shall be possible to move the valve 15 to a closed state via a limited overpressure on a line 7A.

Such an arrangement, without hose (4A) for the expiration gas, provides a significantly smaller compressible volume, smaller than half the volume that needs to be actuated by the lung ventilator.

Figures 3 and 4 illustrate an equipment unit 201 that includes a lung ventilator A and a number of requisite connection hoses, among other things.

As will be seen from Figure 3, the ventilator A has an air intake and a gas (O_2) intake, and the insufflation gas through the hose 3A may consist of pure air, pure O_2-gas or a chosen mixture thereof.

The hose 3A is thus adapted for insufflation gas and is connected to a valve 15.

The hose 3A and all other hoses and electric conductors have been identified with the same reference signs along their full length.

It will be noted, however, that all hoses and conductors/lines will normally have within the equipment unit 201 an internal hose or conductor section that is connected to a two-part coupling unit in one end-wall of the equipment unit, and will include an external hose or conductor section that is connected to a valve, measuring probe or the like.

Figure 3 also shows the known valve (6A in Figure 1) divided functionally so that a part 6A' is included in the ventilator A and functions to apply an overpressure in the hose 7A. This overpressure can be varied between two values and in accordance with the phase of the insufflation gas.

The other part is comprised of the valve 15.

The hose 7A is designed to control the valve 15 from one state to another state with the aid of the valve 6A' and with a controlled overpressure, so as to force insufflation gas into the patient V in one first valve position and to enable expiration gas to pass freely in a second valve position.

This free passage of the expiration gas can take place against an adapted counterpressure (the PEEP-pressure) which may range from 2-20 cm water column for instance.

The hoses 3A and 4D are pressure-measuring hoses for measuring pressure differences and pressure variations generated by a gas flow.

The hose 3C is solely for measuring pressure.

The hose 3E is intended to conduct insufflation gas or expiration gas to an evaluating unit for gas analysis.

The four hoses 3C, 3E, 3D and 4D are together connected to equipment 10 for sensing and evaluating the criteria C, D, E and J. The values obtained are sent to a computer unit 600.

The equipment intended for criteria B, F, G, H and I is also integrated in the equipment unit 201, with their respective evaluating units 2B, 2F, 2G, 2H and 2I connected to the computer unit 600.

It will be evident from this that the equipment unit 201 shall have connected thereto seven external air or gas conducting hose parts or sections 7A, 3A, 3D, 4D, 3C, 3E and 3G, preferably of mutually different cross-sections and/or different orientation, and also an external hose 4B for conducting anaesthesia inducing pharmaceutical, and three external electrical connecting lines 3F, 3H and 3I.

Also connected to the computer unit 600 is a display unit 202, which will be described in more detail below with reference to Figures 5 and 8.

Figure 4 illustrates in perspective an inventive arrangement 200 that includes an equipment unit 201 and associated display unit 202, for anaesthetising a living creature by administering thereto an infused volume of anaesthesia-inducing pharmaceutical per unit of time with the aid, inter alia, of a lung ventilator and an infusion unit with associated control units for regulating the magnitude of

the gas volume or the gas volume and/or the volume of pharmaceutical per unit of time as necessary.

The complete arrangement 200 comprises and/or includes a plurality of external sensors, measuring probes and the like and requisite external hoses or conductor sections in addition to the compact equipment unit 201 and associated display unit 202.

Not all of these sensors and measuring probes are shown, but merely indicated.

An external hose section or an external electrical conductor section shall be capable of detachably connecting respective sensors and measuring probes to the equipment unit 201.

Thus, there is shown in Figures 3 and 4 a number of sensors which are co-ordinated via an external electrical conductor section or via an individual external hose section and each connected via an individual two-part coupling device to a respective connecting part in the end wall 201G of the equipment unit 201. The sensor 13F is connected to the connector part 3F' via an external conductor section.

Pressurised air is delivered to a cuff-like sensor 13G via an external section of the hose 3G and the cuff squeezed or tightened so as to stop the flow of blood. As the pressure of the air is slowly released, the pulsations occurring in the pressurised air are sensed as the blood is again allowed to flow freely.

This section of the hose 3G between the cuff and the equipment unit 201 is connected to a connector part 3G' in the end wall 201g via a two-part connector.

A sensor 13H is connected to a connector 3H' in the end wall 201g via an external electrical conductor section and via a two-part connector, for evaluating the S_pO_2-value.

A sensor 13I is connected to a connector 3I' in the end wall 201g via a two-part connector and via an external electrical conductor section, for evaluating the BIS-values.

These sensors 13F, 13G, 13H and 13I may be of a known kind.

The external sections of the hoses 3A, 3C, 3D, 4D, 3E and 7A are all coupled to a mouth-proximal valve arrangement that includes a valve 15 and a measuring probe 42.

The equipment unit 201 is also designed to include and enclose essential parts of a lung ventilating unit A whose internal hose section for the insufflation hose 3A opens out into a two-part hose coupling that has a connection part 3A' in the end-wall 201g.

Correspondingly, the internal sections of the hoses 7A, 3D, 4D, 3E and 3C are adapted to open out into a respective two-part hose coupling that includes a connector part 7A', 3D', 4D', 3E' and 3C' located in the end-wall 201g.

The invention also allows all or at least selected external sections of all hoses to the valve 15 and the measuring probe 42 to be collected in a single hose bundle 12, with a connecting part 12" adapted for all hose section adapted for fixed but readily removed coaction with the connector parts 7A', 3A', 3D', 4D', 3E' and 3C' in the end-wall part 201g.

The equipment unit 201 is also adapted to include essential parts of said infusion unit B, including the control unit 2B and the actuator part 1B.

The equipment unit 201 is also designed to include and detachably hold a container or vessel 20' belonging to an infusion unit B and containing anaesthesia inducing pharmaceutical 22 in liquid phase, and is also designed to carry said display unit 202.

As before mentioned, there extends between the valve 14 and measuring probe 42 and the equipment unit 201 a hose bundle 12 which includes a plurality of external sections of the hoses used.

Figure 7 shows a proposed cross-section of one such hose bundle 12, from which it will be evident that solely external hose sections for hoses 3A, 3D, 4D, 3C, 3E and 7A are co-ordinated in an exemplifying manner, whereas the hoses 4B and 3G have individual hose coupling 4B', 3G' at the side of the hose coupling common to remaining hoses and including the connecting part or coupling device 12".

As will be seen from Figure 4, there is attached to one end-wall part 201g of the equipment unit 201 a first coupling part of the two-part hose coupling, where

it is indicated that one connecting part 3A' is placed centrally and where the connecting parts 7A', 3D', 4D', 3E' and 3C' are orientated peripherally for coaction with an external hose bundle 12 of given cross-section according to Figure 7.

Anaesthesia inducing pharmaceutical is administered under an adapted pressure via the coupling part 4B', and the NIBP-values are sensed via the coupling part 3G'.

Also mounted on the same end-wall part 201g of the equipment unit 201 are one or more connector parts of one or more electrical connectors, said connector parts being adapted for coaction with one or more external electric cables or conductors that carry electric signals representative of different criteria, such as ECG-values (3F'), SpO_2-values and PLET-values (3H') and BIS-values 3I' respectively.

Figure 5 illustrates a proposed embodiment of a suitable display surface 202' in slightly larger scale than in Figure 4.

The display unit 202 is adapted for co-operation with an arrangement of the kind described in the introduction and the display surface 202' functions to present one or more criteria applicable to a patient in a state of anaesthesia induced by administering to the patient a volume of anaesthesia inducing pharmaceutical per unit of time, by infusion.

It will be seen from the figure, and also from Figure 8, that the display surface 202' is divided into a number of large and small surface areas.

A first surface area 202A is adapted to show the timewise variation of a number of criteria, while a second surface area 202B is adapted to show the instantaneous values of a number of criteria.

The first surface area 202A is adapted to show the timewise variation of a chosen number of criteria, by equally orientating the time axes of a number of criteria in mutually superimposed relationship.

More specifically, four different criteria are shown with the same time axes in the following order: uppermost ECG-values, followed by CO_2-values, followed by PLET-values and then the P-values.

The lowermost field shows the BIS-values with an own time axis.

The second surface area 202B is divided into fields in which a criterion is shown in each field, in an abbreviated form, with the instantaneous value of respective criteria shown adjacent thereto.

Figures 5 and 8 illustrate in all desirable clarity that an uppermost field 81 discloses the NIBP-value and the RR-values, the next following field 82 discloses the $EtCO_2$ and RR values, the next following field 83 discloses the SpO_2-value and the FiO_2-value, the next following field 84 discloses VL and the P-values, and that the next following field 85 discloses the value Vinf concerning the volume of applied anaesthesia inducing pharmaceutical, while a field 86 shows the mean BIS-value in percent. The display also includes a field 87 for the Poccl-value, the value of the pressure in container 20'.

More particularly, it is proposed in accordance with the present invention that one or more first criteria related to one or more diagnostic units, and one or more second criteria related to one or more therapeutic units are allowed to be presented on a display unit or a display surface, that one or more of said first criteria is/are selected for display on said display surface as instantaneous values, and that one or more of said first criteria is/are selected for display on said display surface as the timewise variation of the criterion.

One or more of said second criteria are chosen for display on the display surface as instantaneous values, and one or more of said second criteria are chosen for display on said display surface as the timewise variation of the criterion.

In the case of some criteria chosen for display as the timewise variation of the criterion, the time axes are co-ordinated and arranged in superimposed relationship.

In order to obtain concordance of the time axes and instantaneous values, it is necessary with respect to some criteria to delay sensor-related signals, for instance through the medium of time delay circuits 2C', 2D', 2F' and 2H' with mutually adapted time delays.

It is also proposed that the instantaneous values and/or graph-related values of one or more criteria related to one or more diagnostic units, and/or corresponding values of one or more criteria related to one or more therapeutic units are stored in the computer memory so that the instantaneous values can be

shown as timewise variation of the criterion and the graph-related values shown as compressed trends when necessary.

Referring back to Figure 4, it will be seen that the display unit 202 is rotatably mounted on and readily removed from the front part 201a of the equipment unit 201 and above a container 20' that contains anaesthesia inducing pharmaceutical 22 and which can be actuated by the control circuit of the infusion unit.

A control unit for regulating the volume of anaesthesia inducing pharmaceutical administered per unit of time can be actuated through the medium of an activating device positioned adjacent to and above the container.

One or more control circuits for regulating other criteria, such as criteria relating to the lung ventilator, can be actuated via activating means positioned adjacent to and on one side of said container 20', these activating means being referenced 210.

It is also possible within the scope of the invention to allow one or more control circuits included in the control unit for regulating chosen criteria to be actuated through the medium of activating means orientated in one or more rows, such as within a third surface area of the display unit referenced 202C in Figure 4.

The equipment unit 201 also includes regulating means which are activated via the computer unit and which function to regulate a value of a chosen criterion and/or keep said value constant.

Figure 6 shows schematically a valve arrangement 15 and an adjacent measuring probe 42 for controlling lung ventilation and for measuring different criteria relating to the administered insufflation gas, and when necessary also criteria relating to the expiration gas.

Figure 7 is a cross-sectional view of an external hose bundle 12 whose one end is able to co-act with the equipment 12 via a coupling device 12", while the other end of said hose bundle 12 is adapted for coaction with the valve 15 and the measuring probe 42.

For instance, it will be seen from Figure 7 that the hose bundle 12 has a large hose cross-section for the connection 3A' and the hose 3A, a hose cross-section for connection 7A' and the hose 7A, a hose cross-section for the connection 3D' and the hose 3D, a hose cross-section for the connection 4D' and the

hose 4D, a hose cross-section for the connection 3E' and the hose 3E, and a hose cross-section for the connection 3C' and the hose 3C.

Figure 8 is a schematic block diagram showing another proposed embodiment of the mutually co-acting parts and circuits enclosed in the equipment unit 201, wherewith certain of said parts and circuits can be controlled and monitored by a computer unit 600 that has associated programs and storage units.

This embodiment is based on the concept of co-ordinating requisite evaluating units included in utilised units to be included in a common computer unit 600. A person skilled in this art will be able to produce on the basis of the above description software and a control system adapted to the aforementioned functions, and it is therefore deemed unnecessary to describe the necessary programming to any greater extent in this document.

Where possible, the reference signs given in Figure 3 have also been used in Figure 8 to identify corresponding function blocks.

The lung ventilator A has also been described in connection with the circuits that require pressure and flow in order to determine desired criteria through the medium of said circuits. These have been shown and described with reference to the lung ventilator.

It should be mentioned that the majority of the function block shown in Figure 8 for selected criteria are known to the art, and will not therefore be described in greater detail.

Thus, Figures 3 and 8 show that the occurrence/presence of and the value of chosen criteria are delivered to a central or common computer unit 600 which is connected to the display unit 202 via a line 600A which is adapted for two-way information, so that the computer unit 600 is able to transmit desired values to the display unit 202, while the third surface area 202C can be used to send instructions and messages to the computer unit 600 which changes the conditions of said criteria on the basis of these signals.

It is applicable to both embodiments that structuring of the instantaneous values presented on the display unit are field-related in the manner shown in the enlarged view of Figure 5.

With regard to the surface area 202C, it can be mentioned that alarm limits can be entered and evaluated via manual actuation of the surface section -Alarm Limits-of the surface area 202C, that certain measurement values can be presented over a long time period (the time axis is extended) via the surface section -TRENDS-, calibration can be effected via -CAL-, certain measurement values can be presented via -SETUP-, and the timewise variation can be frozen for closer assessment via -FREEZE-.

The display surface 202' has a fourth surface area 202D in which other relevant information is presented, such as malfunctioning and/or an alarm.

Both of the aforedescribed embodiments incorporate different time delays for compensation of so-called lag time.

In order to achieve timewise-correct indication of several criteria it is necessary to delay rapidly evaluatable criteria so that said criteria can be displayed on the display at the same moment in time as criteria that are evaluated more slowly.

For instance, it can be assumed that the CO_2-value and the O_2-value for criterion E is the last value to appear with respect to time, and consequently it is necessary to delay other criteria over an adapted time period, so that these values will appear simultaneously in co-ordination on the display surface. In practice, the delay concerned will be shorter than one second.

Consequently, equipment corresponding to equipment 2C, 2D, 2F and 2H include adapted time delay circuits 2C', 2D', 2F' and 2H', which are preferably individually adapted.

The computer equipment 600 of both embodiments may be equipped with an -expert system-, where a utilised computer program is adapted to sense and calculate and interpret obtained measurement values and also to set alarm limits.

The computer program of the Figure 8 embodiment is referenced 601.

A computer program 602 may be adapted to control received measurement values against set point values in a closed-loop-sequence.

Computer program 603 may be used to change the limit values for adapted criteria in accordance with the patient's weight, sex, race, etc.

The information displayed on the display surface can be transferred to another display screen with the aid of a computer program 604 and also with the aid of the telecommunications network, such as over the Internet.

Although the invention has been described with reference to the use of a sole infusion unit B, it will be understood that two or more such units can be used, with the same or mutually different pharmaceutical.

The lung ventilator A can be duplicated so that one unit is used for each individual lung, therewith enabling separate control of insufflation and expiration.

It is also proposed that therapy control is effected through the medium of keys and knobs and the equipment unit 201, while diagnostic control can be effected via the display unit 202.

The two illustrated and described embodiments of the invention are also based on the assumption that the various parts of the equipment unit are mutually co-ordinated with respect to communication via a computer unit provided in the equipment unit, and that said computer unit is adapted to monitor unit-related criteria and patient-related criteria.

The computer unit 600 is also adapted to distinguish between therapeutic criteria and diagnostic criteria through the medium of therapeutic units and diagnostic units included in said equipment unit, said therapeutic and diagnostic units being co-arranged on a printed circuit board included in the equipment unit and, when applicable, having function units mounted thereon, wherewith an input to respective units is connected internally to one part of a two-part coupling device with said part attached to the end-wall of said equipment unit.

For instance, it can be mentioned that an ECG-board or card has a construction that requires three (3) connection electrodes with each electrode having a respective external conductor section.

The CO_2-board and O_2-board has a gas analysing unit mounted thereon.

Both boards are connected to a separately mounted sampling pump.

It will be understood that the invention is not restricted to the aforedescribed and illustrated exemplifying embodiments thereof and that modifications can be made within the scope of the inventive concept as illustrated in the accompanying claims.

CLAIMS

1. An arrangement for anaesthetising a living creature and maintaining said creature anaesthetised, by administering to said creature an infused volume of an anaesthesia inducing pharmaceutical in liquid phase per unit of time with the aid of one or more lung ventilator units and one or more infusion units, and including first means for monitoring unit-related criteria and second means for monitoring creature-related criteria, **characterized** in that selected parts of the lung ventilator unit, with the exception of insufflation hose, expiration valve, measuring probe and a number of hoses, and selected parts of the infusion unit, with the exception of cannula and hose, are mutually combined to form an equipment unit; in that some of said parts of said equipment unit are mutually co-ordinated with respect to communication via a computer unit included in the equipment unit; and in that said computer unit is adapted to monitor unit-related criteria and creature-related criteria.

2. An arrangement according to claim 1, **characterized** in that said computer unit is adapted to distinguish between therapeutic criteria and diagnostic criteria, through the medium of therapeutic units and diagnostic units included in said equipment unit.

3. An arrangement according to claim 1 or 2, **characterized** in that a therapeutic unit and/or a diagnostic unit is structured on a printed circuit board or card, which when applicable has a function unit or units mounted thereon; in that several of said boards or cards are co-ordinated in the equipment unit, with one input of respective units connected to one part of a two-part coupling device, wherewith said parts are attached to and co-ordinated on the equipment unit.

4. An arrangement according to claim 3, **characterized** in that the coupling parts belonging to said equipment unit are comprised of one or more hose couplings and one or more electrical connections.

5. An arrangement according to claim 3, **characterized** in that an external hose part coupled to the lung ventilator unit and a number of other external hose parts are collected in a hose bundle.

6. An arrangement according to claim 5, **characterized** in that said hose bundle includes a hose part for insufflation gas, a hose part for controlling a creature-proximal expiration valve, two hose parts for measuring pressure difference, a hose part for measuring pressure and/or a hose part for sampling gas.

7. An arrangement according to claim 1, **characterized** in that said infusion unit includes a container or vessel which encloses an anaesthesia inducing pharmaceutical in liquid phase and which can be releasably held by the equipment unit.

8. An arrangement according to claim 3, **characterized** in that a measuring probe, sensor or like device separate from the equipment unit can be connected to the coupling parts belonging to said equipment unit via a hose part or an electrical conductor.

9. An arrangement according to claim 8, **characterized** in that said measuring probe, sensor or like device includes electronic circuits which are adapted to sense/detect creature related criteria and to determine the value of such criteria.

10. An arrangement according to claim 1, **characterized** in that said equipment unit has connected thereto and/or affixed thereto a display unit which is adapted for the display of one or more instantaneous criteria values and/or timewise variation of the criterion on a display surface.

11. An arrangement according to claim 1 or 10, **characterized** in that one or more first criteria related to one or more diagnostic units, and one or more second criteria related to one or more therapeutic units can be presented on a display surface of the display unit; in that one or more of said first criteria is/are chosen for

display on said display surface as instantaneous values; and in that one or more of said first criteria is/are chosen for display on said display surface as timewise variation of the criterion.

12. An arrangement according to claim 11, **characterized** in that one or more of said second criteria is/are chosen for display on the display surface as instantaneous values; and in that one or more of said second criteria is/are chosen for display on said display surface as timewise variation of the criterion.

13. An arrangement according to claim 11 or 12, **characterized** in that the time axes of certain criteria chosen to be shown as timewise variation of respective criteria are co-ordinated and arranged in mutually superimposed relationship.

14. An arrangement according to claim 11, 12 or 13, **characterized** in that the signals generated by a measuring probe, sensor and like device in respect of some chosen criteria are time-delayed prior to said criteria being presented on the display surface.

15. An arrangement according to claim 11 or 12, **characterized** in that instantaneous values and values concerning time-related graphs for one or more criteria-related to one or more diagnostic units and/or instantaneous values and values concerning time-related graphs for one or more criteria related to one or more therapeutic units can be stored in memories for presentation as timewise variation of the respective criteria as required.

16. An arrangement according to claim 15, **characterized** in that the timewise variation of respective criteria can be presented in a time compressed form.

17. An arrangement according to claim 1, **characterized** in that the control unit associated with the lung ventilator unit is either connected to a computer unit or included therein.

18. An arrangement according to claim 1 or 5, **characterized** in that a first part of a two-part hose coupling is attached to the equipment unit, wherewith said coupling part is not solely adapted for coaction with an external hose section for an insufflation gas flow, but also to a number of other external hose sections.

19. An arrangement according to claim 1, **characterized** in that one or more first parts of one or more two-part hose couplings is/are attached to the equipment unit, wherewith said first coupling parts are adapted for co-action with one or more units for evaluating different criteria, such as CO_2-content, O_2-content, breathing frequency and like criteria, and/or for pressure actuation of an expiration valve.

20. An arrangement according to claim 1, **characterized** in that the equipment unit has attached thereto one or more first parts of one or more two-part electric connectors, wherewith said first parts are adapted for coaction with one or more external electric cables that carry sensor-related electric signals representative of different criteria, such as ECG-values, SpO_2-values, BIS-values, PLET-values.

21. A display unit adapted for coaction with an arrangement according to any one of the preceding claims, on which there can be presented one or more criteria relating to a living creature that has been anaesthetised by administering a volume anaesthesia inducing pharmaceutical in liquid phase by infusion per unit of time, **characterized** in that a first surface area of the display surface of the display unit is adapted to display the timewise variation of a number of criteria; and in that a second surface area of said display surface is adapted to display instantaneous criteria values.

22. A display unit according to claim 21, **characterized** in that the first surface area is adapted to display the timewise variation of a chosen number of criteria, by choosing mutually identical time axes and orientating said axes in superimposed relationship.

23. A display unit according to claim 21, **characterized** in that the timewise variation of at least one (or more) of said criteria is (are) displayed in the surface area over a longer period of time than other criteria.

24. A display unit according to claim 23, **characterized** in that the time axis is compressed in the event of a time duration that exceeds said longer time duration.

25. A display unit according to claim 21, **characterized** in that the second surface area is divided into fields to enable respective criteria to be displayed in respective fields, e.g. in an abbreviated form, with the instantaneous value of respective criteria displayed adjacent thereto.

26. An arrangement according to any one of claims 1-20 that includes a display unit according to any one of claims 21-25, **characterized** in that said display unit is rotatably mounted on the front part of the equipment unit and above a container which contains anaesthesia inducing pharmaceutical and which can be actuated by the control unit of said infusion unit.

27. An arrangement according to claim 26, **characterized** in that the control circuit belonging to the control unit and functioning to regulate the volume of anaesthesia inducing pharmaceutical administered per unit of time can be actuated via activating means belonging to said equipment unit and positioned adjacent said container.

28. An arrangement according to claim 26, **characterized** in that the control circuit belonging to said control unit for regulating criteria related to the lung ventilator can be actuated via activating means positioned adjacent said container.

29. An arrangement according to claim 26, **characterized** in that control circuits for regulating further criteria can be actuated via activating means orientated in one or more rows within a third surface area of the display surface.

30. An arrangement according to claim 1 or claim 26, **characterized** in that the computer unit in the equipment unit includes activatable regulating circuits adapted for holding a value of one or more chosen criteria constant.

31. An arrangement according to claim 1 or claim 26, **characterized** in that said equipment unit is adapted to include or to carry a readily removed display unit.

Fig. 1

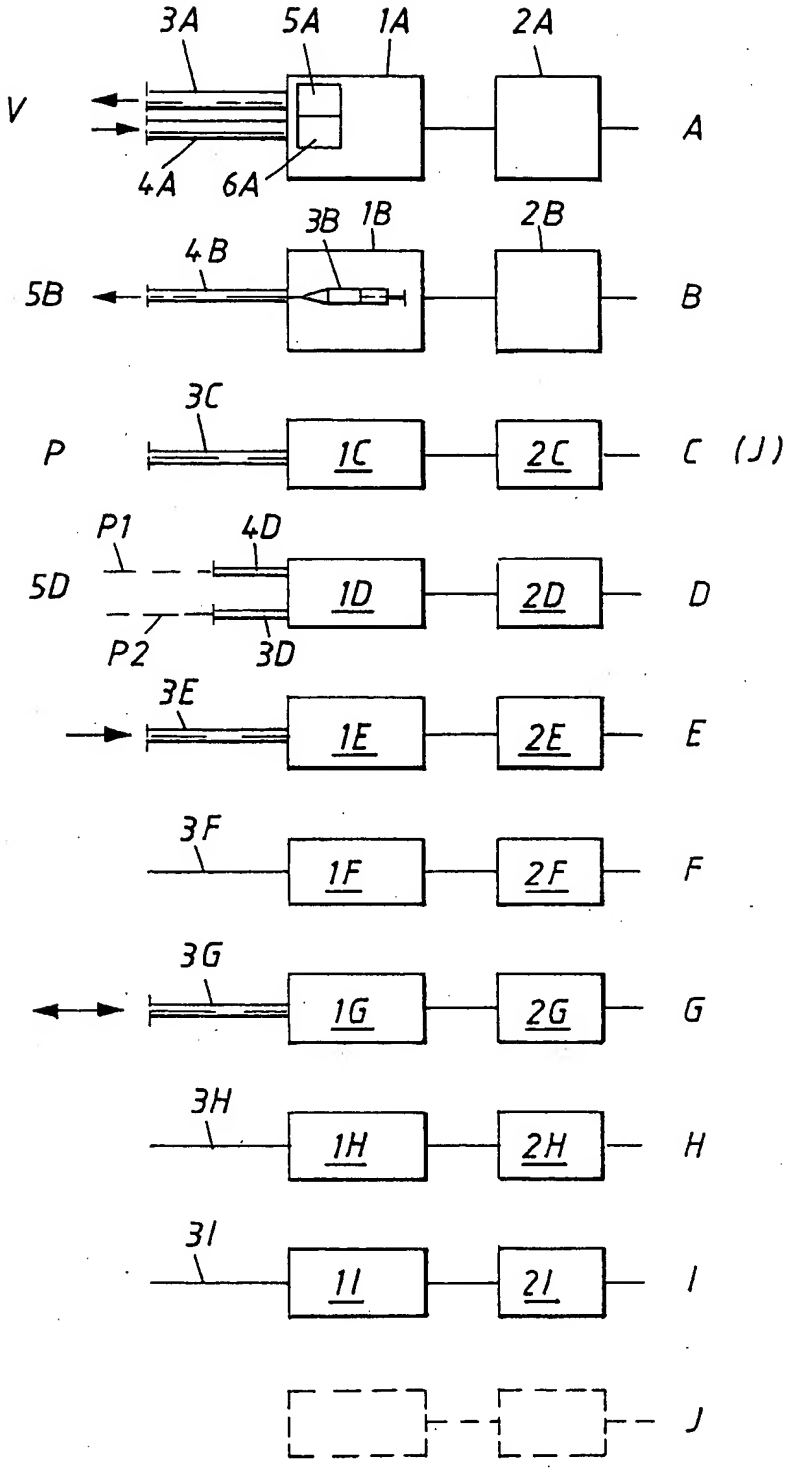
3A
5A
1A
2A
V
A
4A
6A
3B
1B
2B
4B
5B
B
3C
P
1C
2C
C (J)
P1
4D
5D
1D
2D
D
P2
3D
3E
1E
2E
E
3F
1F
2F
F
3G
1G
2G
G
3H
1H
2H
H
3I
1I
2I
I
J

Fig. 2

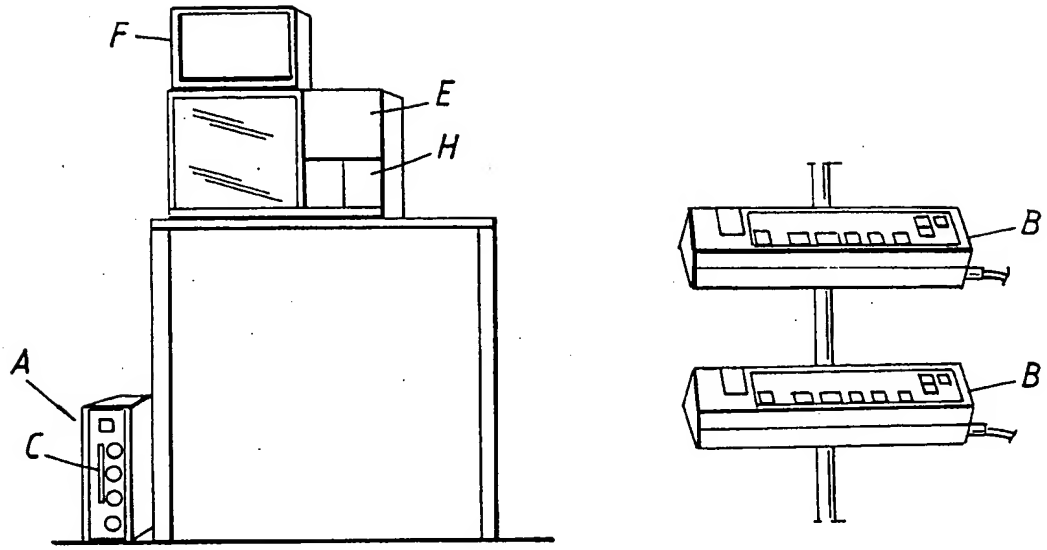
F
E
H
A
C
B
B

Fig. 5

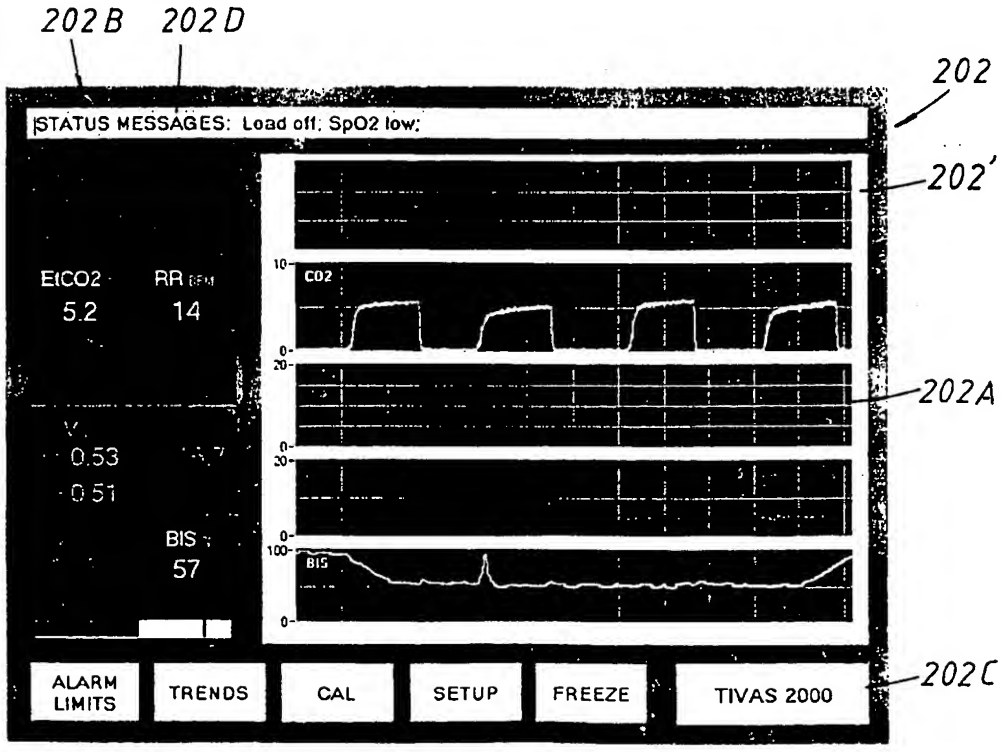
202B
202D
202
202'
STATUS MESSAGES: Load off; SpO2 low;
EtCO2
5.2
RR
14
0.53
0.51
BIS
57
CO2
BIS
202A
ALARM LIMITS
TRENDS
CAL
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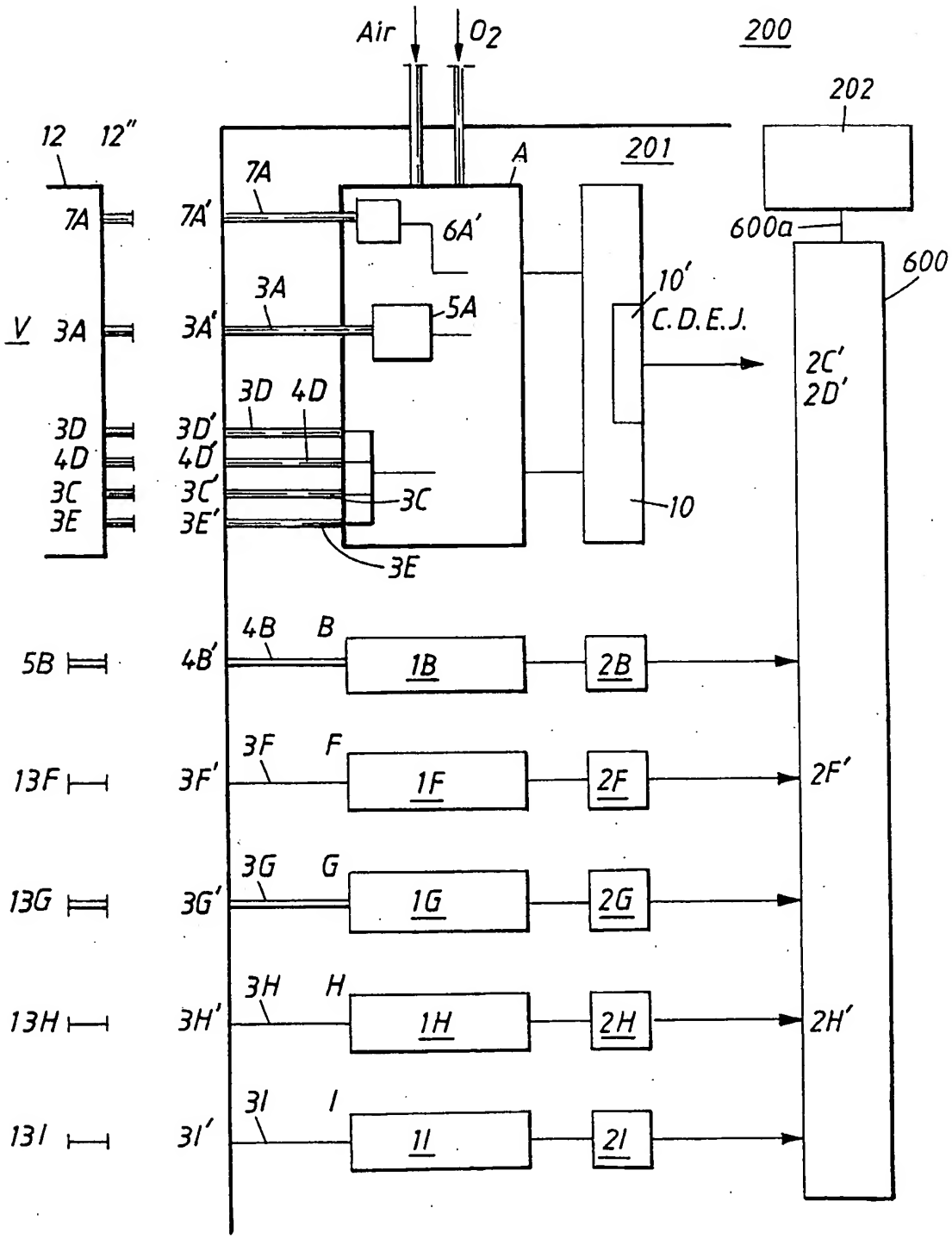
Fig. 3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13F
1F
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2F'
3G
G
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13G
1G
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I
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1I
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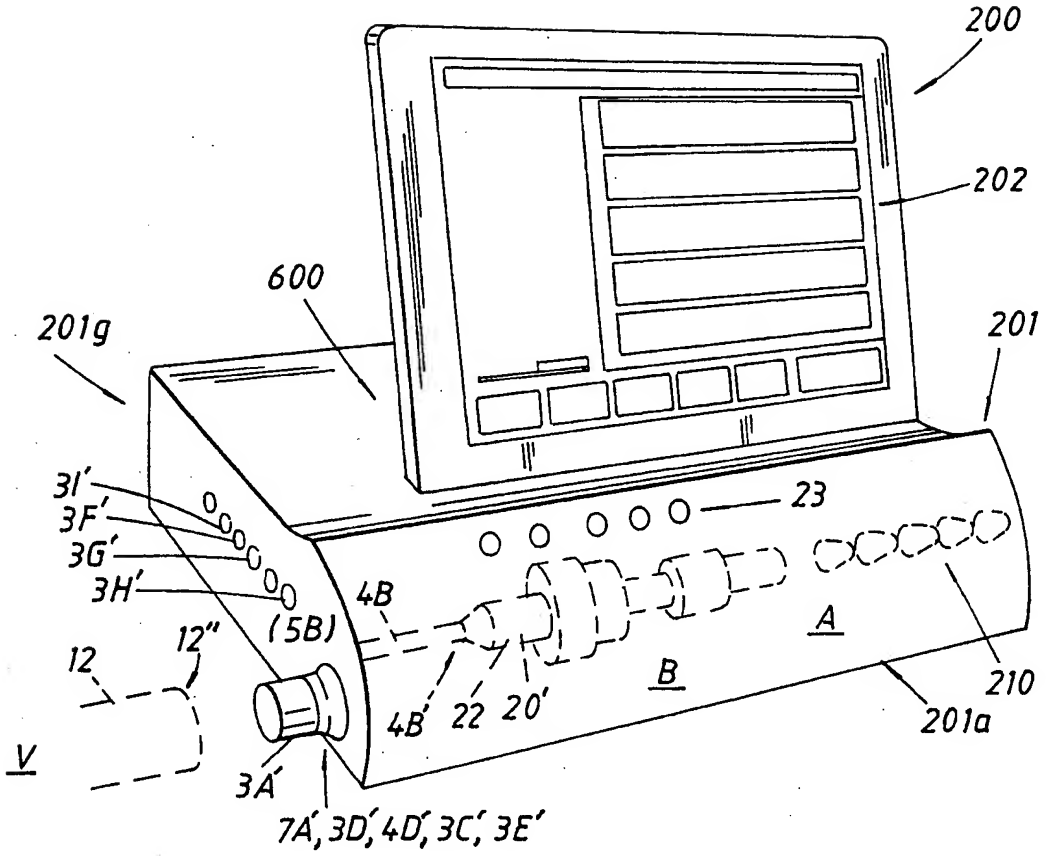
Fig. 4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3A'
7A', 3D', 4D', 3C', 3E'

Fig. 6

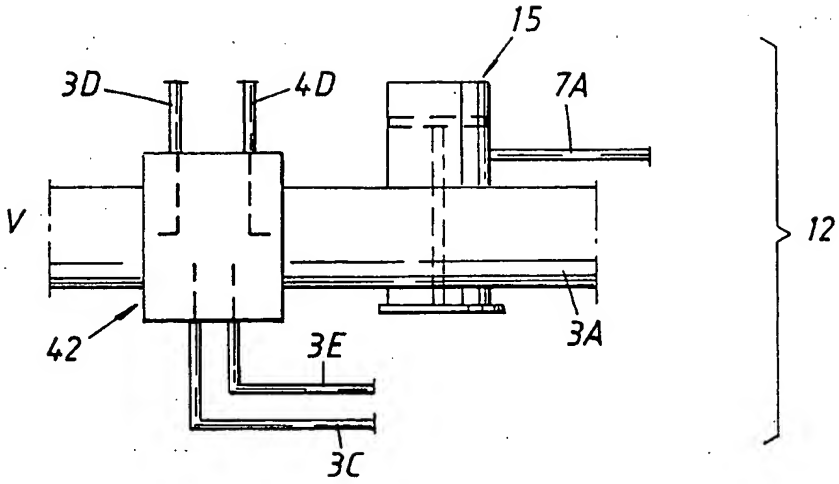


Fig. 7

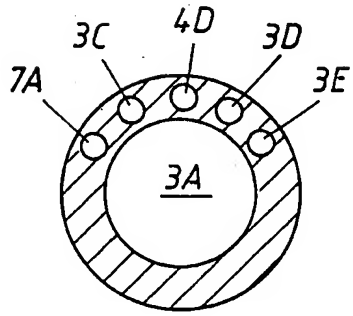
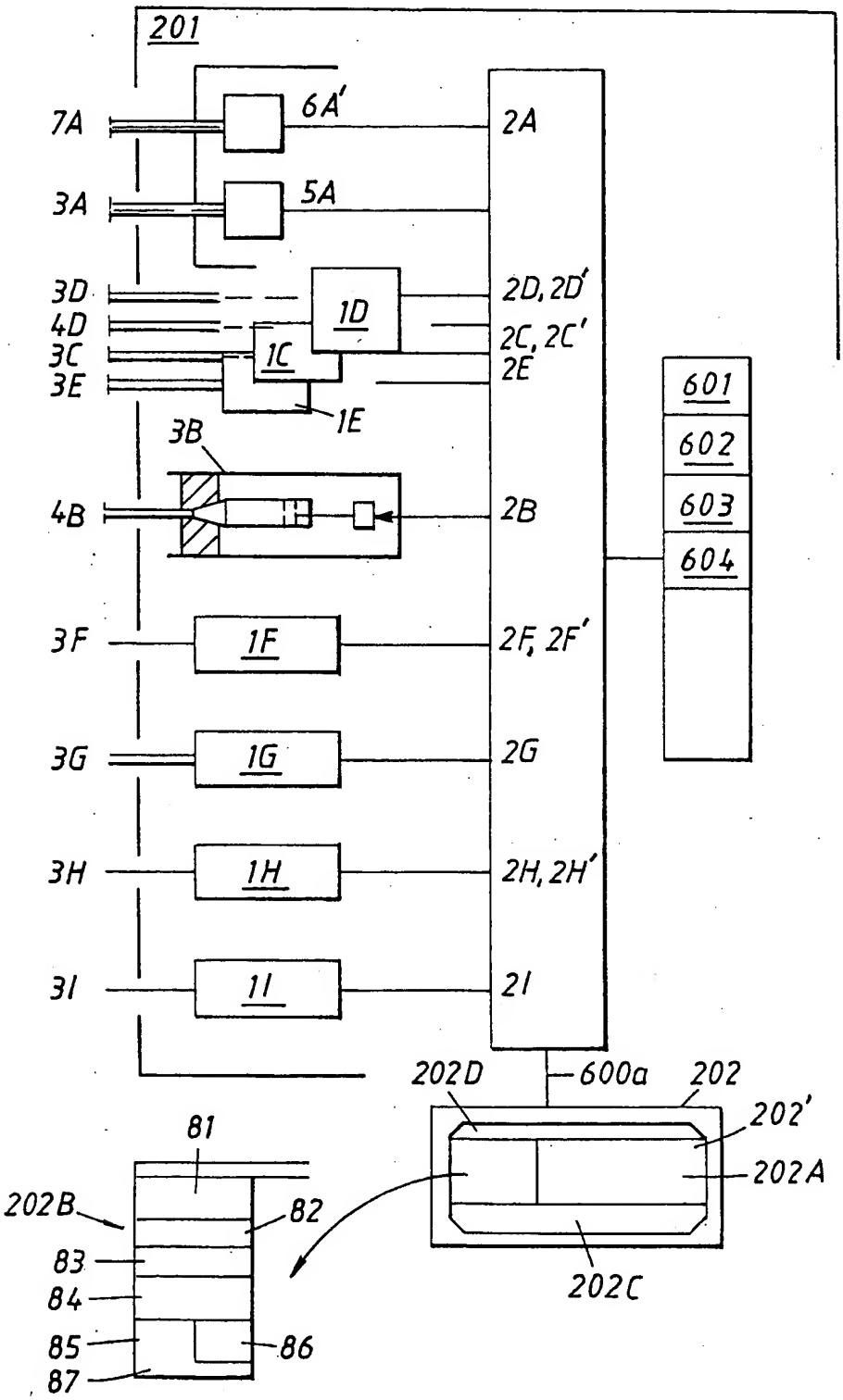


Fig. 8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3I
1I
2I
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202'
202A
202C
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202B
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00910

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61M 5/00, A61M 16/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5007688 A (J. BAYERLEIN ET AL.), 16 April 1991 (16.04.91), column 1, line 6 - column 3, line 33, figure 3 -- --------	1-20,26-31

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2000	16 -10- 2000
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Cilla Lyckman/Js Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00910

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims 1-20 and 26-31 concern an arrangement for anaesthetising a living creature and maintaining the creature anaesthetised with the aid of one or more lung ventilators and infusion units. The lung ventilators and infusion units are combined to form an equipment unit.
2. Claims 21-25 concern a display unit with a first and a second surface area adapted to display the timewise variation of a number of criteria and instantaneous criteria values respectively.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-20, 26-31

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/08/00

International application No.
PCT/SE 00/00910

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5007688 A	16/04/91	DE 3815273 A	16/11/89
		FR 2630909 A	10/11/89

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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WO 02/094099 A1

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09/861,878 21 May 2001 (21.05.2001) US

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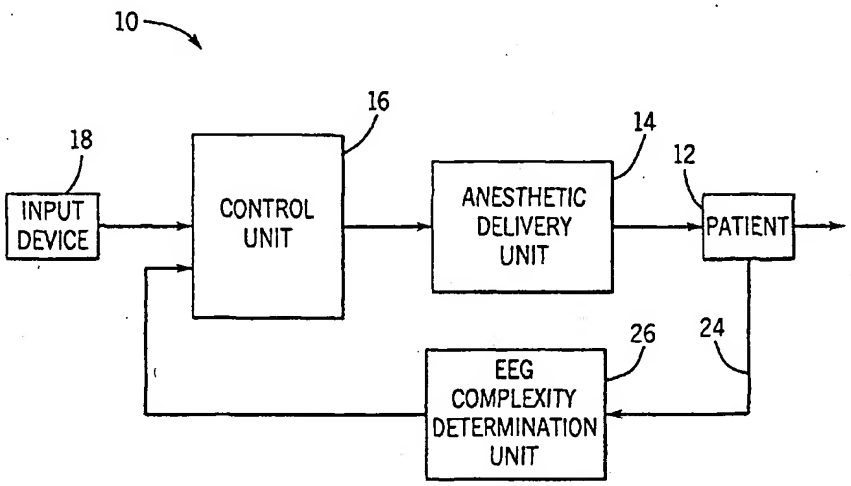
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

[Continued on next page]

(54) **Title:** CLOSED LOOP DRUG ADMINISTRATION METHOD AND APPARATUS USING EEG COMPLEXITY FOR CONTROL PURPOSES



(57) **Abstract:** A closed loop method and apparatus for controlling the administration of an hypnotic drug to a patient. Electroencephalographic (EEG) signal data is obtained from the patient. At least one measure of the complexity of the EEG signal data is derived from the data. The complexity measure may comprise the entropy of the EEG signal data. The EEG signal data complexity measure is used as the feedback signal in a control loop for an anesthetic delivery unit to control hypnotic drug administration to the patient in a manner that provides the desired hypnotic level in the patient. An EEG signal complexity measure obtained from the cerebral activity of the patient can be advantageously used in conjunction with a measure of patient electromyographic (EMG) activity to improve the response time of hypnotic level determination and of the feedback control of drug administration. A pharmacological transfer function may be used, along with pharmacokinetic and pharmacodynamic models.

WO 02/094099 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

CLOSED LOOP DRUG ADMINISTRATION METHOD AND APPARATUS USING EEG COMPLEXITY FOR CONTROL PURPOSES

CROSS REFERENCE TO RELATED APPLICATION

The present application claims the priority of U.S. provisional application 60/291,873, filed May 18, 2001.

BACKGROUND OF THE INVENTION

The present invention is directed to a method and apparatus for controlling the administration of an hypnotic drug in "closed loop" fashion.

An hypnotic drug may comprise an anesthetic agent and the hypnotic state induced in a patient by the administration of such a drug is one of anesthetization. An hypnotic drug typically acts on the brain to produce a lessening or loss of consciousness in the patient. The extent to which the patient is anesthetized is often termed the "hypnotic level" or "depth of anesthesia." In the present invention, the existing hypnotic level, or depth of anesthesia, in the patient is sensed and used to control the hypnotic drug administration to the patient in the manner of a closed loop, or feedback, regulator to achieve and maintain a desired level in the patient.

More particularly, the present invention employs the complexity of electroencephalographic (EEG) data obtained from the patient as a sensed indication of the hypnotic level of the patient for use in controlling hypnotic drug administration. The use of such an indication provides closed loop control of drug administration that is based on an accurate assessment of the hypnotic condition of the patient and one that is highly responsive to changes in that condition. Such an indication can be made rapidly responsive to changes in the hypnotic condition of the patient.

Hypnotic drugs, or anesthetic agents, are administered by inhalation or intravenously. When administration is by inhalation, the anesthetic agent comprises a volatile liquid that is vaporized in a vaporizer. The vaporized anesthetic agent is entrained in breathing gases for the patient. The concentration of the anesthetic agent supplied by the vaporizer is determined by the anesthesiologist by manipulating appropriate controls on the vaporizer. The concentration of anesthetic agent in the lungs of the patient may be measured by measuring the amount of anesthetic agent contained in the breathing gases

exhaled by the patient at the end of the exhalation phase of the respiratory cycle, i.e. the end tidal concentration (ET_{conc}). Typical inhaled anesthetic agents are sevoflurane, enflurane, and desflurane, among others.

In a simple form, intravenous administration of an hypnotic drug may employ a syringe that injects the drug into a vein of the patient. For extended administration, a motor driven syringe or a motor driven infusion pump may be employed. A commonly used, intravenously administered, anesthetic agent is propofol.

In addition to hypnosis, high quality anesthesia must also consider loss of sensation (analgesia), muscle relaxation, suppression of the autonomous nervous system, and blockage of the neuro muscular function. This may require administration of a number of different drugs via the same or different routes. Further, different hypnotic drugs and/or different administration routes may be used at different stages of an anesthetization or a medical procedure. For example, hypnosis may be introduced by an intravenously administered drug and maintained by an inhaled drug.

In the process by which a drug, including a hypnotic drug, takes its effect in the body, two aspects are important: pharmacokinetics and pharmacodynamics. Pharmacokinetics deals with the effect of the body on the drug, such as the body's absorption, distribution or diffusion, metabolism, and excretion of the drug. Pharmacokinetics describes how the drug is distributed in the course of time from the site of delivery to different parts of the body and to a particular organ in which the drug is supposed to have its effect.

For use in the study of drugs, the determination of dosages, and the like, mathematical models have been developed for the pharmacokinetics of a drug. Because of the complexity of the physiology of the body, the models are typically based on theoretical compartments, such as plasma, fat, or the brain. Pharmacokinetic models typically allow for consideration of anthropometric data, such as patient height, weight, age, sex, etc. Pharmacokinetic models are available for hypnotic drugs, or anesthetic agents, including propofol, based on two or more different compartments. See Shafer, et al. Anesthesiology, 1998; 69:348-356 describing a two compartment model for propofol.

When a specific effect of a drug can be directly or indirectly measured, such data can be used to define a pharmacodynamic model of the drug with respect to its concentration at the site at which it is effective, i.e. effect-site concentration. Such models

may also use anthropometric data. For hypnotic drugs the effect is the hypnotic state of the patient and the effect-site in the brain.

In a broad sense, all hypnotic drug administration is of a controlled loop nature. In a basic form, an anesthesiologist administers such a drug to a patient, observes the state of the patient resulting from the administration of the drug, and then maintains or alters the dose based on his/her observations. However, in a more specific sense, reflecting recent work in the field of anesthesia, closed loop control relates to the sensing of the hypnotic state of the patient by some form of instrumentation and automatically controlling the administration of the drug responsive to a feedback signal from the instrumentation. The term is used herein in the more specific sense.

The interest in closed loop control is posited, at least in part, on a desire to accurately establish the hypnotic level or depth of anesthesia of the patient. If the anesthesia is not sufficiently deep, the patient may maintain or gain consciousness during a surgery, or other medical procedure, resulting in an extremely traumatic experience for the patient, anesthesiologist, and surgeon. On the other hand, excessively deep anesthesia reflects an unnecessary consumption of hypnotic drugs, most of which are expensive. Anesthesia that is too deep requires increased medical supervision during the surgery recovery process and prolongs the period required for the patient to become completely free of the effects of the drug.

Rapidity is another desirable feature of an hypnotic drug administration control system. Fast response is particularly desirable should the patient approach consciousness since, as noted above, unexpected emergence is to be avoided, but is rendered more likely as excessively deep anesthesia is avoided.

A closed loop hypnotic drug delivery system has been described using the bispectral index as a control parameter. See Mortier E., et al. Anesthesia, 1998, August; 53 (8):749-754. See also published European Patent Application No. EP 959,921 to authors of this article. The bispectral index is proprietary to Aspect Medical Systems of Farmingham, MA and is described in one or more of the following U.S. Patents: 4,907,597; 5,101,891; 5,320,109; and 5,458,117. The bispectral index is an effort to form a single variable, termed the bispectral index (BIS), that correlates behavioral assessments of sedation and hypnosis over a range of anesthesia for several hypnotic drugs.

The bispectral index comprises three components that are combined in

various ways to provide an indication over a range of hypnotic levels from light sedation to deep anesthesia. See Ira R. Rampil, "A Primer for EEG Signal Processing in Anesthesia", Anesthesiology 89 (1998), 980-1002. See also U.S. Patent application, Serial No. 09/688,891 to an inventor named herein and another, assigned to a common assignee, also containing a description of this index.

In order to compute a BIS value, measured EEG data over a period of fifteen seconds is used. During anesthesia, the level of painful stimulation can vary drastically and cause rapid changes in the hypnotic level of the patient, i.e. wake the patient up. Because of the time required to compute a BIS value, the bispectral index may not be sufficiently rapid to warn the anesthesiologist that this is occurring. Also, the bispectral index is contaminated by electromyographic (EMG) activity which may lead to misjudgment of the hypnotic level of a patient. See Bruhn J., et al., Anesthesiology 2000; 92:1485-7. Certain paradoxical behavior of the bispectral index (BIS) not connected to EMG has also been reported; see Detsch O. et al., British Journal of Anesthesia 84 (1):33-7 (2000); Hirota K. et al., Eur J Anaesth 1999, 16, 779-783.

Another approach to closed loop or feedback control of hypnotic drug administration is disclosed in published International Patent Appln. WO 98/10701 by Mantzaridis, et al. In the technique of the patent, the patient is fitted with headphones and is subjected to noise in the form of "clicks" of one ms duration at a frequency of 6.9 Hz. The auditory evoked potential (AEP) resulting from this stimulation, and more particularly, the alteration of the delay between the auditory stimulus and the auditory stem response in the brain is used in this method to evaluate the level of hypnosis of a patient during anesthesia. While an AEP index has been shown to distinguish between the conscious and unconscious states of a patient in an accurate manner, the correlation with drug concentration is not as good and has been reported as poorer than that for the bispectral index. See Doi M, et al., Br J Anaesth. 1997, Feb.; 78(2):180-4. The auditory response does not persist to the lowest hypnotic levels, restricting the range of measurement. This tends to lessen the utility of the AEP index for use in closed loop hypnotic drug administration. Also, the technique requires placing earphones on the patient and is limited to patients having adequate hearing.

U.S. Patent 6,016,444 to E. R. John, describes another method using information extracted from EEG signal data to control a closed-loop drug delivery system.

The parameters mentioned include EEG spectral powers measured in different frequency ranges and the spectral edge frequencies, below which are found, for example, 50% or 90% of the total power spectrum. In addition to the EEG spectrum derived parameters, the method also uses brain wave evoked responses, such as brain stem or cortical auditory evoked responses, which may bear a correlation to anesthesia level. Electrodes are applied to the front and back of the scalp and the method essentially compares the derived features between these locations using covariance matrices. After the patient has been anesthetized and when he/she has obtained the plane of anesthesia desired by the anesthesiologist, a form of calibration procedure called "self-normalization" is carried out. The plane of anesthesia is determined by clinical signals observed by the anesthesiologist. After self-normalization, the system tries to maintain the anesthetic level of the patient established during that procedure as the set point.

The need for the self-normalization procedure presents a disadvantage to this procedure in that the anesthesiologist may forget to carry it out or carry it out at the wrong plane of anesthesia. In the time period required for the procedure, which according to the patent preferably lasts for 60 seconds, the condition of the patient may change. Also, there is no published evidence that the particular EEG-derived parameters chosen for measurement correlate very well with hypnotic levels.

BRIEF SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide an improved method and apparatus for controlling the administration of an hypnotic drug to a patient in closed loop fashion that employs an accurate and highly responsive indication of the hypnotic condition of the patient, thereby to improve the administration of the drug. The indication used in the present invention can be made rapidly responsive to changes in the hypnotic condition of the patient. This is particularly advantageous in alerting an anesthesiologist that the patient may be emerging from an anesthetized state to a conscious state.

It is a further object of the present invention to provide a closed loop control method and apparatus which is capable of operating over a wide range of hypnotic conditions in the patient ranging from no hypnosis, i.e. consciousness, to deep hypnosis or anesthesia.

The method and apparatus of the present invention is simple to set up,

employing a simple array of electrodes on the head of the patient. No self-normalization procedure as required in earlier disclosed techniques, is required with the technique of the present invention.

Briefly, in the present invention, electroencephalographic (EEG) signal data is obtained from the patient. For this purpose, one or more pairs of biopotential electrodes may be applied to the forehead of the patient. At least one measure of the complexity of the EEG signal data is derived from the data. The complexity measure of the EEG signal data may comprise the entropy of the EEG signal data. An EEG signal complexity measure obtained from the cerebral activity of the patient can be advantageously used in conjunction with a measure of patient electromyographic (EMG) activity resulting from the muscle activity of the patient to improve the response time of hypnotic level determination and of the feedback control of drug administration. The EEG signal data complexity measure is used in as the feedback signal in a control loop for an anesthetic delivery unit to control hypnotic drug administration to the patient in a manner that provides the desired hypnotic level in the patient.

A plurality of EEG signal data complexity measures may be used in determining the hypnotic level of the patient, if desired.

To improve the control of hypnotic drug administration, the present invention may employ a transfer function relating to the pharmacological effects of the drug in the patient and the manner, or other characteristics of, its administration. Pharmacokinetic and pharmacodynamic models may be employed in establishing the transfer function.

The control of drug administration provided by the present invention may be improved by the use of additional data obtained from the patient, such as his/her cardiovascular characteristics or the end tidal concentration of volatile hypnotic drugs.

Information pertinent to the anesthetization of the patient, such as patient characteristics, hypnotic drug type, particular medical procedure and physician, may be inputted or stored for use in carrying out the control of drug administration. Information generated during course of an anesthetization may also be employed in controlling the administration of the hypnotic drug to the patient.

Various other features, objects, and advantages of the invention will be made apparent from the following detailed description and the drawings.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING

In the drawing:

Fig. 1 is a schematic diagram showing one embodiment of a closed loop drug administration control using EEG complexity for control purposes;

Fig. 1A is partial schematic diagram of a component of the control shown in Fig. 1;

Fig. 2 shows one form for the placement of electrodes on a patient;

Fig. 3 is a schematic diagram showing a modification of the control in Fig. 1; and

Fig. 4 is another schematic diagram showing a further modification of the control shown in Fig. 1.

DETAILED DESCRIPTION OF THE INVENTION

In the present invention, a quantification of the complexity of the EEG signals obtained from the patient is used to determine his/her hypnotic level and, in turn, to control the administration of a hypnotic drug to the patient in a closed loop fashion. This approach is based on the premise that neuronal systems, such as those of the brain, have been shown to exhibit a variety of non-linear behaviors so that measures based on the non-linear dynamics of the highly random EEG signal allow direct insight into the state of the underlying brain activity. EEG biopotential signals are obtained from electrodes applied to the head of the patient.

There are a number of concepts and analytical techniques directed to the complex nature of random and unpredictable signals. One such concept is entropy. Entropy, as a physical concept, describes the state of disorder of a physical system. When used in signal analysis, entropy addresses and describes the complexity, unpredictability, or randomness characteristics and information content of a signal. In a simple example, a signal in which sequential values are alternately of one fixed magnitude and then of another fixed magnitude has an entropy of zero, i.e. the signal is totally predictable. A signal in which sequential values are generated by a random number generator has greater complexity and a higher entropy.

Applying the concept of entropy to the brain, the premise is that when a person is awake, the mind is full of activity and hence the state of the brain is more non-linear, complex, and noise like. Since EEG signals reflect the underlying state of brain

activity, this is reflected in relatively more "randomness" or "complexity" in the EEG signal data, or, conversely, in a low level of "order." As a person falls asleep or is anesthetized, the brain function begins to lessen and becomes more orderly and regular. As the activity state of the brain changes, this is reflected in the EEG signals by a relative lowering of the "randomness" or "complexity" of the EEG signal data, or conversely, increasing "order" in the signal data. When a person is awake, the EEG data signals will have higher entropy and when the person is asleep the EEG signal data will have a lower entropy.

With respect to anesthesia, an increasing body of evidence shows that EEG signal data contains more "order", i.e. less "randomness", and lower entropy, at higher concentrations of an hypnotic drug, i.e. a lower hypnosis level or greater depth of anesthesia, than at lower concentrations. At a lower concentration of hypnotic drug, the EEG signal has higher entropy. This is due, presumably, to lesser levels of brain activity in the former state than in the latter state. See "*Stochastic complexity measures for physiological signal analysis*" by I.A. Rezek and S.J. Roberts in IEEE Transactions on Biomedical Engineering, Vol. 4, No. 9, September 1998 describing entropy measurement to a cut off frequency of 25 Hz and Bruhn J, et al. "*Approximate Entropy as an Electroencephalographic Measure of Anesthetic Drug Effect during Desflurane Anesthesia*", Anesthesiology, 92 (2000), pgs. 715-726 describing entropy measurement in a frequency range of 0.5 to 32 Hz. See also Viertiö-Oja H, et al. "*New method to determine depth of anesthesia from EEG measurement*" in J. Clin. Monitoring and Comp. Vol. 16 (2000) pg. 16 which reports that the transition from consciousness to unconsciousness takes place at a universal critical value of entropy which is independent of the patient. See also Zhang XS et al., Med. Bio. Eng. Comput. 1999, 37:327-34.

In sum, the following can be said. First, certain forms of entropy have generally been found to behave consistently as a function of hypnotic or anesthetic depth. See Bruhn J, et al. Anesthesiology 92 (2000) 715-26; Anesthesiology 93 (2000) 981-5 and Viertiö-Oja H, et al. "*Entropy of EEG signal is a robust index for depth of hypnosis*", Anesthesiology 93 (2000) A, pg. 1369. This warrants consideration of entropy as a natural and robust choice to characterize levels of hypnosis. Also, because entropy correlates with depth of anesthesia at all levels of anesthesia, it avoids the need to combine various subparameters as in the bispectral index (BIS). Second, it has been

found that the transition from consciousness to unconsciousness takes place at a critical level of entropy which is independent of the patient. See Viertio-Oja H, et al. in J. Clin. Monitoring and Computing, Vol. 16 (2000) pg. 16. Thirdly, and of particular practical significance, recovery of a patient toward consciousness from anesthesia can often be predicted by a rise of entropy toward the critical level.

A number of techniques and associated algorithms are available for quantifying signal complexity, including those based on entropy, as described in the Rezek and Roberts article in IEEE Transactions on Biomedical Engineering. One such algorithm is that which produces spectral entropy for which the entropy values are computed in frequency space. Another algorithm provides approximate entropy which is derived from the Kolmogorov-Sinai entropy formula and computed in Taken's embedding space. See Steven M. Pincus, Igor M. Gladstone, and Richard A. Ehrenkranz, "*A regularity statistic for medical data analysis*", J. Clin. Monitoring 7 (1991), pgs. 335-345. A program for computing approximate entropy is set out in the Bruhn et al., article in Anesthesiology. The spectral entropy and approximate entropy techniques have found use in analyzing the complexity of EEG signals.

Another technique for non-linear analysis of highly random signals is expressed in Lempel-Ziv complexity in which the complexity of a string of data points is given by the number of bytes needed to make the shortest possible computer program which is able to generate the string. See Abraham Lempel and Jacob Ziv, "*On the complexity of finite sequences*", IEEE Trans., IT-22 (1976) pgs. 75-81.

A still further approach that may be applied to EEG signal analysis is fractal spectrum analysis based on chaos theory. In fractal spectrum analysis, the EEG signal is divided into a harmonic component and a fractal component. The harmonic component includes the simple frequencies whereas the fractal component contains the part which is invariant under scaling in time. It has been found that the fractal exponent Beta which corresponds to the frequency power law $1/f^{\beta}$ increases consistently in the course of deepening anesthesia. See Viertiö-Oja, H. et al. in J Clinical Monitoring and Computing, Vol. 16 (2000), pg. 16.

The use of spectral entropy to characterize the amount of complexity or disorder in an EEG signal is deemed advantageous because of its computational simplicity. The use of spectral entropy to obtain a diagnostic index indicative of the

depth of anesthesia or hypnotic level of a patient is described in detail in the aforesaid U.S. patent application 09/688,891 which is incorporated herein by reference in its entirety.

The complexity measurement derived from EEG signal data can be combined with a more rapidly obtainable measure derived from electromyographic (EMG) signals. EMG signals result from the activity of the muscles and exist as long as the muscles are not paralyzed. With the measurement of electromyographic (EMG) activity contained in the biopotentials from electrodes on the forehead of the patient, as the level of anesthesia approaches inadequacy, a painful stimulus to the patient causes a contraction of the frontalis muscle (frowning) which can be detected as peaks in EMG signal amplitude. This reaction can often be observed substantially before the pain eventually brings the patient to consciousness. EMG signals can thus provide an early warning sign to the anesthesiologist to increase the administration of hypnotic drug(s) in order to prevent consciousness and awareness during surgery. The measure derived from the EMG signals may comprise spectral power data.

Both the EEG and EMG signals are typically obtained from the same set of electrodes applied, for example, to the forehead of the patient so that the signals from the electrodes contain both types of data. The EEG signal component dominates the lower frequencies (up to about 30 Hz) contained in the biopotentials existing in the electrodes and EMG signal component dominates the higher frequencies (about 50 Hz and above).

Importantly, because of the higher frequency of the EMG signals, the sampling time can be significantly shorter than that required for the lower frequency EEG signals. This allows the EMG data to be computed more frequently so that a combined EEG-EMG diagnostic indicator of hypnotic level or depth of anesthesia can quickly indicate changes in the state of the patient.

In one approach to providing such a diagnostic index, the EEG signals and the EMG signals can be separately analyzed and thereafter combined into the diagnostic index or indicator. As noted above, because of the celerity with which changes in the anesthetic state of the patient can be determined from the EMG signals, the overall index can quickly inform the anesthesiologist of changes in the state of the patient. For example, the response time for computing the hypnotic level of the patient from the

complexity of the EEG signal is approximately 5-30 seconds whereas the data derived from the EMG signal and the diagnostic index can be fully updated every 0.5 seconds.

In another approach, the spectral range of the complexity computations, i.e. entropy computations, is widened to extend into the EMG range. Thus, the spectral range over which the complexity computations are carried out to provide an indicator may extend from some lower frequency of, for example 0.5 to 7 Hz, up to a frequency above 32 Hz. To filter out power line interference, the spectral range may be divided into bands with the elimination of frequencies around 50, 60 Hz and 100, 120 Hz. For example, in an embodiment in which the spectral range extends to approximately 150 Hz, a lower frequency band (0.5 - 47 Hz) will contain mostly EEG activity while two upper bands (63 - 97 Hz and 123 - 147 Hz) will include primarily EMG activity. The use of a widened frequency range does not require a division of the spectrum into two segments as does the first approach because all components in the widened frequency range are treated in the same manner. And, any boundary within the spectral range would be artificial since the frequency bands for the EEG and EMG signals are overlapping.

Further, the complexity measurement obtained in this second approach can be updated as often as is permitted by the higher frequencies of the EMG signals in the widened spectral range of the complexity computation. This will provide a very current indication to the anesthesiologist of the depth of anesthesia of the patient.

The indicator obtained from the signal complexity computation over the widened spectral range can be used in conjunction with a complexity measurement obtained only from the EEG portions of the frequency spectrum to provide useful information to the anesthesiologist regarding what portion of the indicator comes from cerebral activity and what portion comes from muscle activity. This is particularly important in cases in which muscle tension is enhanced for some reason. An example that is frequently encountered is with opioid anesthesia that is often used in heart operations. The extensive use of opioids has the side effect of high muscle rigidity that persists after loss of consciousness. If the BIS is used, this results in misleadingly high values of the BIS. Distinction of the complexity measurement obtained only from the EEG portions of the frequency spectrum from the signal complexity over the widened spectral range shows this situation clearly.

Fig. 1 schematically shows control apparatus 10 for supplying an hypnotic drug to patient 12. For control purposes, apparatus 10 employs EEG signal data complexity as an indication of the hypnotic level existing in the patient. As used herein, the term "EEG signal data" may be taken to mean data obtained from cerebral activity of the patient, i.e. so-called "pure EEG signals", either without or with data obtained from muscle activity, i.e. EMG signals.

The hypnotic drug may be supplied to patient 12 by anesthesia delivery unit 14. If the drug is administered intravenously anesthetic delivery unit 14 may comprise a motor driven infusion pump. For hypnotic drugs administered by inhalation, anesthesia delivery unit 14 is typically a vaporizer. As noted above, it is common to use both types of hypnotic drugs and differing anesthetic delivery units in the course of an anesthetization. The amount of hypnotic drug delivered by anesthetic delivery unit 14 is controlled by control unit 16, typically by controlling its infusion or administration rate.

In Fig. 1, an input signal to control apparatus 10 is provided by input device 18 operated by the anesthesiologist. For example, the anesthesiologist may establish a value corresponding to the hypnotic level to be achieved in patient 12 and the input device would provide an appropriate input signal to control unit 16. Or, the anesthesiologist may input a value corresponding to a specific desired dosage, if for example control 10 is operated in an open loop fashion. Input device 18 or control unit 15 may establish related criteria such as the minimum and maximum dosages or defined delivery rates of hypnotic drug to be delivered by control 10.

To determine the hypnotic state existing in patient 12, electrodes 20 may be applied to the forehead of patient 12 as shown in Fig. 2. Electrodes 20 receive electroencephalographic (EEG) signals from patient 12. The electrodes also receive electromyographic (EMG) signals from the forehead of patient 12. Electrodes 20 are connected to conductors 22 which may be formed into cable 24.

Cable 24 is connected to EEG complexity determination unit 26. Unit 26 includes a protection circuit which is operative in the event the patient is subjected to electro-surgery or cardiac defibrillation, an analog digital converter, and a bandpass filter. Unit 24 also contains one or more computational elements, such as a microprocessor, that performs artifact detection and removal and determines the spectral entropy or other characterization of the amount of complexity or disorder in the EEG

signal obtained from electrodes 20, as well as spectral power data derived from the EMG signal data obtained from the electrodes, thereby to provide EEG signal data.

The output of EEG complexity determination unit 26 comprises a diagnostic index or other value indicative of the complexity or disorder of the EEG signal data. As noted above, it is deemed preferable for reasons of reducing response times, particularly in sensing the emergence of the patient from the hypnotic state, to incorporate data from EMG signals in such a diagnostic index or value. It may also be advantageous to provide more than one index. For example, indices in which signal complexities have has been computed over different frequency ranges may be used. The output from EEG complexity determination unit is provided to a further input of control unit 16 as shown in Fig. 1 to complete a control loop in control 10.

In a simple embodiment of the invention shown in Fig. 1, control logic 16, may be seen as a comparator 28, as shown in Fig. 1A. Comparator 28 compares the reference signal generated by input device 16 with the feedback signal provided by EEG complexity determination unit 24 and provides an output signal corresponding to the difference between the two inputs. This output signal may be applied to control logic or signal processor 30, the output of which forms the output signal to anesthetic delivery unit 14 for use in controlling the amount of hypnotic drug delivered to patient 12 and hence his/her hypnotic level.

The hypnotic level existing in patient 12, as ascertained by EEG complexity determination unit 26, is driven toward that corresponding to the input signal from input device 18 by the action of the control loop in control 10 in the well known manner of a closed loop or feedback regulator. The polarity of the reference and feedback inputs to comparator 26 are shown in Fig. 1A to graphically connote this control action. Specifically, the closed loop control apparatus incorporating control unit 16 acts in a manner to drive the difference between the reference signal from input unit 18 and the feedback signal from EEG complexity determination unit 26, and hence the output signal from control unit 16, to zero. For example, and starting at a zero input signal difference and output signal condition, if the hypnotic level of the patient elevates, or moves towards consciousness, the complexity of the EEG signal data will increase, as will the input signal from complexity determination unit 26 to the positive input of comparator 28. This will produce a positive output from control unit 16 to anesthetic

delivery unit 14, which may be taken as a symbolic indication that a greater quantity of hypnotic drug should be administered to patient 12 by anesthetic delivery unit 14 to restore the hypnotic level to a lower value. The greater amount of drug so delivered will decrease the hypnotic level in the patient and cause it to move toward that established by the reference signal from input device 18. The decrease in the hypnotic level also causes the input signal from complexity determination unit to decrease to restore the input signal difference to zero. The converse is true if the hypnotic level of the patient moves towards a greater state of unconsciousness. That is, as patient 12 moves to a greater degree of unconsciousness, the output signal from EEG complexity determination unit 24 will decrease. When compared to the reference signal from input device 16, this will cause the output signal from comparator 26 to assume a symbolic negative value, indicative of a reduction in the amount of hypnotic drug to be supplied to patient 12 from anesthetic delivery unit 14 thereby allowing the level of unconsciousness of the patient to rise back to the desired value.

As shown in Fig. 3, to improve the administration of the hypnotic drug and to enhance patient safety, additional physiological data may be obtained from patient 12 for use in the operation of the closed loop control. For example, it is known that many, if not most of the drugs used in anesthesia, affect, sometimes severely, the cardiovascular status of the patient. Propofol is known to induce a drop of systemic blood pressure in patients, whereas desflurane can induce a significant increase in heart rate. This may have a significant impact on patients particularly sensitive to such changes of vital function such as elderly patients, critically ill patients, and diabetic patients. To this end, cardiovascular parameters, such as heart rate, blood pressure, blood oxygen saturation, and cardiac output, can be obtained by appropriate instrumentation 32 and supplied as a feedback signal to control unit 16a. Desired, or reference, values for these parameters may be inputted by an appropriate input device 18a, along with or separate from an hypnotic level reference values, to alter the output of control unit 16a to anesthetic delivery unit 14 so that the administration of the hypnotic drug to patient 12 is carried out in a manner to preserve these vital functions. The cardiovascular parameters may be used to alter the input signals provided to control unit 16a or a separate control loop responsive to desired and actual cardiovascular data may be provided inside of or outside of the control loop employing the EEG signal data

complexity to, for example, limit the delivery rate of a drug or provide a specific combination of intravenous and volatile drugs.

Also as shown in Fig. 3, anesthetic delivery unit 14 may comprise an intravenous infusion pump 14a and a vaporizer 14b, for intravenously administered and inhaled hypnotic drugs, respectively. Pump 14a and vaporizer 14b may be controlled in coordinated fashion by control unit 16a.

As further shown in Fig. 3, when an inhaled hypnotic drug is administered to patient 12, as by use of vaporizer 14b, the end tidal drug concentration (ET_{conc}) exhaled by patient 10 may be measured by sensor 34 and supplied as a feedback signal to control unit 16a to provide a feedback control that ensures that the amount of hypnotic drug received by the patient corresponds to that commanded by the input to vaporizer 14b from control unit 16a. The concentration of hypnotic drug in the end tidal breathing gases of the patient corresponds to the concentration in the lungs of the patient and, therefore to that in the breathing gases provided to patient 12 by vaporizer 14b and is thus useful as a feedback signal.

Fig. 4 shows a modification of the control unit for the closed loop control apparatus shown in Fig. 1. As noted above, the pharmacology resulting from the administration of a drug depends to a considerable extent on the pharmacodynamic and pharmacokinetic properties of the drug. This is particularly true of a hypnotic drug that is not delivered directly into the effect-site. That is, an intravenously supplied hypnotic drug, such as propofol, is delivered to the venous blood of the patient whereas its effect occurs in the brain. For an inhaled drug that is delivered to the respiratory tract of the patient, somewhat more information is available as the concentration of the gas in the lung, which can be measured, is in steady state proportional to the concentration in arterial blood. Therefore, less pharmacokinetic modeling is required as the blood compartment concentration can be obtained from measurements.

In the embodiment of the invention schematically shown in Fig. 4, a transfer function generator 50 may be used to improve the drug administration by control 10. Transfer function generator 50 establishes a desired relationship between the measured hypnotic level in patient 12, as characterized by the degree of complexity in the EEG signal data, and the rate or other characteristics of drug administration by anesthetic delivery unit 14. It also establishes a relationship between EEG signal data complexity

and the clinical endpoints of hypnosis levels. In establishing the transfer function, a pharmacokinetic model 52 and pharmacodynamic model 54 for the drug may be employed. These models typically comprise algorithms describing the interaction between the hypnotic drug and a patient stored in, and employed by, a computer. The output of transfer function generator 50 is provided to control logic 30a in control unit 16b for use in its operation in the provision of an output signal to anesthetic delivery unit 14. For this purpose, control unit 16b, in addition to a comparative function, may comprise other control or computational elements, such as microprocessors, in control logic 30a. Control logic 30a may provide data, such as the state of its regulation, regulatory routines, or the various signal magnitudes in control unit 16b to models 52 and 54. In cases where a volatile hypnotic drug has been administered to the patient either alone or in addition to an intravenous drug, its concentration, as determined by the end tidal fraction ET_{conc}, may be provided to control unit 16b and to pharmacokinetic model 54 to permit less complicated pharmacokinetic modeling. Cardiovascular parameter data may also be provided to one or more of the models to improve the operation of the models and control 10 and patient safety.

Pharmacokinetic model 52 allows the hypnotic drug to be administered in such a way that its relative concentration in a given compartment, i.e. the brain, can be maintained generally stable, or constant at that which produces the desired hypnotic level. This stability brings a major advantage for both the patient and the anesthesiologist since once an efficient level of drug effect has been reached, the drug level, and hence the hypnotic level will remain constant, thereby to avoid changes in the patient condition, such as regaining consciousness. However, since an hypnotic drug's real effect cannot be fully predicted for a given patient due to pharmacogenetics and because of the variability among individuals of pharmacokinetics models, the use of pharmacodynamic model 54, in addition to pharmacokinetic model 52 and the determination of EEG signal data complexity by unit 26 allows for both the determination of the appropriate effect-site concentration, i.e. the concentration to achieve a given hypnotic level and hence EEG signal data complexity level, as well as a steady state drug level. Where needed for both the models, the "effect" of the hypnotic drug can be measured by evaluating the complexity of the EEG signal data, particularly that originating from the cerebral portion of the EEG signal data.

Also, as shown in Fig. 4, a programmed data source 56 can be provided in control unit 16b for use in operation of control 10. In addition to the input relating to the hypnotic level, source 56 may be used to generate and input data specific to a given anesthetization, including the patient's anthropometrics, such as weight, age, height, sex, body mass index, and the like. The data may also include information identifying the drug that is being administered to the patient. Other data that may be entered at source 56 include information pertaining to the duration of the procedure, the intensity of the surgery, minimum and maximum drug administration levels and/or rates, upper and lower hypnosis level limits and cardiovascular parameters, and the like. Such data could also include information regarding the pattern of surgical intensity likely to be encountered by the patient according to the type of surgery and/or the technique to be employed by the surgeon, and the idiosyncrasies of the surgical practice of a given surgeon. Information of this and other types can be inputted on an individual basis by an anesthesiologist or stored and retrieved from a database of preset surgical information. Such information may also be provided to models 52 and 54, via control logic 30a for use in their operation.

Programmed data in source 56 may also include timing data. This data may be used by control unit 16b to establish a stable, set complexity level for the EEG data signal, and hence hypnotic level in patient 12, for a predetermined period of time. Or, the programmed data may be such that the anesthesiologist could operate program data source 58 so that control 10 is operated in a manner to wake the patient after a preset time as for example, by setting up a "wake-up after ten minutes" routine in source 56. Responsive to inputs provided from data source 56, control logic 30a would then establish the required drug administration rates and timing for anesthetic delivery unit 14 to patient 12 to obtain this effect and timing. An analogous procedure could be carried out with respect to the administration of the hypnotic drug to induce unconsciousness, i.e. loss of consciousness in patient 12 at a point in time in the future. Such features are advantageous for cost savings in terms of operating room usage times, amounts of drug used, and the like.

The transfer function generator 50, as well as models 52, 54, may be supplied with information from a database storage device 58. Such a storage device will typically retain reusable data, such as standard data or stored patient data inputted to the

storage device or inputted, or developed by control 10. This will enable patient data obtained during a prior anesthetization to be reused should the patient require a subsequent anesthetization with the same drug. If desired, transfer function generator 58 may also store information of the type described above in connection with source 56, such as patient type, nature of the surgery, surgical intensity, patterns, drug interaction, etc.

Also, control 10 can record a time series of measured and computed patient information to compute, after enough data is recorded, a patient's specific profile that, thereafter, can be used to predict the behavior of the patient for any particular change of drug delivery rate, as by use of models 52 and 54.

It will be appreciated that, for safety reasons, the control will include appropriate means to allow the anesthesiologist to manually control the delivery of the hypnotic agent, by operation of an input device, by direct intervention at the anesthetic delivery unit, or in same other effective manner.

It is recognized that other equivalents, alternatives, and modifications aside from those expressly stated, are possible and within the scope of the appended claims.

CLAIMS

1. A method for administering an hypnotic drug to a patient, said method comprising the steps of:

(a) establishing a desired hypnotic level to be provided in the patient;

(b) administering the hypnotic drug to the patient;

(c) obtaining EEG signal data from the patient;

(d) deriving at least one measure of the complexity of the EEG signal data;

(e) determining the hypnotic level existing in the patient from the complexity of the EEG signal data;

(f) comparing the hypnotic level existing in the patient to the desired hypnotic level; and

(g) controlling the administration of the hypnotic drug to the patient in accordance with the comparison of step (f).

2. The method according to claim 1 wherein step (d) is further defined as measuring an entropy of the EEG signal data.

3. The method according to claim 2 wherein step (d) is further defined as measuring the spectral entropy of the EEG signal data.

4. The method according to claim 2 wherein step (d) is further defined as measuring the approximate entropy of the EEG signal data.

5. The method according to claim 1 wherein step (d) is further defined as employing a Lempel-Ziv complexity measure.

6. The method according to claim 1 wherein step (d) is further defined as carrying out a fractal spectrum analysis to measure the complexity of the EEG signal data.

7. The method according to claim 1 further defined as deriving a

plurality of EEG signal data complexity measures for use in determining the hypnotic level of the patient and controlling the administration of the hypnotic drug to the patient.

8. The method according to claim 1 wherein step (c) is further defined as obtaining EEG signals resulting from the cerebral activity of the patient for use in the derivation of the measure of step (d).

9. The method according to claim 8 wherein step (c) is further defined as obtaining EMG signals resulting from the muscle activity of the patient and the method further includes the step of deriving a measure of patient EMG activity for use with the derived measure of EEG signal complexity in controlling the administration of the hypnotic drug to the patient.

10. The method according to claim 9 wherein the step of deriving the measure of patient EMG activity is further defined as deriving the measure from a frequency domain power spectrum of the EMG signals.

11. The method according to claim 8 wherein step (c) is further defined as obtaining EMG signals resulting from the muscle activity of the patient and step (d) further includes the step of deriving a measure of the complexity of EEG signal data over a frequency spectrum incorporating the EEG signals and EMG signals for use with the derived measure of the EEG signal complexity in controlling the administration of the hypnotic drug to the patient.

12. The method according to claim 1 further including the steps of establishing desired cardiovascular characteristics for the patient; obtaining cardiovascular data from the patient; comparing the cardiovascular data of the patient to desired cardiovascular characteristics; and further controlling the administration of the hypnotic drug in accordance with the comparison of cardiovascular characteristics and data.

13. The method according to claim 1 further including the step of

establishing a transfer function between the pharmacological effects of the hypnotic drug in the patient and the administration of the drug to the patient for use in controlling the drug administration.

14. The method according to claim 1 further including the step of employing a pharmacokinetic model in controlling the administration of the drug to the patient.

15. The method according to claim 1 further including the step of employing a pharmacodynamic model in controlling administration of the drug to the patient.

16. The method according to claim 15 further including the step of employing a pharmacokinetic model in controlling the administration of the drug to the patient.

17. The method according to claim 13 further including the step of employing a pharmacokinetic model in establishing the transfer function for controlling the administration of the drug to the patient.

18. The method according to claim 13 further including the step of employing a pharmacodynamic model in establishing the transfer function for controlling administration of the drug to the patient.

19. The method according to claim 17 further including the step of employing a pharmacodynamic model in establishing the transfer function for controlling administration of the drug to the patient.

20. The method according to claim 1 further including the step of measuring amounts of volatile hypnotic drugs in breathing gases in the patient and controlling the administration of the hypnotic drugs in accordance with the volatile drug measurement.

21. The method according to claim 13 further including the step of measuring amounts of volatile hypnotic drugs in breathing gases in the patient and as employing the measurement in establishing the transfer function for use in controlling the administration of the drug.

22. The method according to claim 13 further including the steps of obtaining cardiovascular data from the patient and as employing the cardiovascular data in establishing the transfer function for use in controlling the administration of the hypnotic drug.

23. The method according to claim 1 further including the step of providing information relating to one or more of the patient, the hypnotic drug, a medical procedure, and a physician for use in controlling the administration of the hypnotic drug to the patient.

24. The method according to claim 1 further including the step of storing information relating to one or more of the patient, the hypnotic drug, a medical procedure, and a physician for use in controlling the administration of the hypnotic drug to the patient.

25. The method according to claim 24 wherein the stored information includes information relating to a previous anesthetization of the patient.

26. The method according to claim 23 further including the step of storing information relating to one or more of the patient, the hypnotic drug, a medical procedure, and a physician and as employing the stored information in controlling the administration of the hypnotic drug to the patient.

27. The method according to claim 1 including the step of generating information in the course of an anesthetization and employing the generated information in controlling the administration of the hypnotic drug to the patient.

28. Apparatus for administering an hypnotic drug to a patient, said apparatus comprising:

(a) means for establishing a signal corresponding to a desired hypnotic level for the patient;

(b) an anesthetic delivery unit for administering the hypnotic drug to the patient;

(c) a sensor for obtaining EEG signal data from the patient;

(d) means coupled to said sensor for deriving at least one measure of the complexity of the EEG signal data, for determining the hypnotic level existing in the patient from the complexity of the EEG signal data, and for providing a signal corresponding to same; and

(e) a control unit including a comparator having inputs coupled to said elements (a) and (c) and an output coupled to element (b), said comparator comparing the signals corresponding to the hypnotic level existing in the patient and the signal corresponding to the desired hypnotic level and providing an output signal for controlling the anesthetic delivery unit and the administration of the hypnotic drug in accordance with the comparison.

29. The apparatus according to claim 28 wherein element (d) is further defined as means for measuring an entropy of the EEG data to determine the hypnotic level existing in the patient.

30. The apparatus according to claim 29 wherein element (d) is further defined as means for measuring the spectral entropy of the EEG signal data.

31. The apparatus according to claim 29 wherein element (d) is further defined as means for measuring the approximate entropy of the EEG signal data.

32. The apparatus according to claim 28 wherein element (d) is further defined as means employing a Lempel-Ziv complexity measure to determine the hypnotic level existing in the patient.

33. The apparatus according to claim 28 wherein element (d) is further defined as means for carrying out a fractal spectrum analysis to measure the complexity of the EEG signal data to determine the hypnotic level existing in the patient.

34. The apparatus according to claim 28 wherein element (d) is further defined as deriving a plurality of EEG signal data complexity measures for determining the hypnotic level existing in the patient.

35. The apparatus according to claim 28 wherein element (c) is further defined as a sensor for obtaining EEG signals resulting from the cerebral activity of the patient and element (d) is further defined as using EEG signals in providing the signal corresponding to the hypnotic level existing in the patient.

36. The apparatus according to claim 35 wherein element (c) is further defined as a sensor for obtaining EMG signals resulting from the muscle activity of the patient and element (d) is further defined as deriving a measure of EMG activity from the EMG signals and using same with a measure derived from EEG signal complexity to provide the signal corresponding to the hypnotic level in the patient.

37. The apparatus according to claim 36 wherein element (d) is further defined as means for obtaining a frequency domain power spectrum of the EMG signals to derive the measure of EMG activity in the patient.

38. The apparatus according to claim 35 wherein element (c) is further defined as a sensor for obtaining EMG signals resulting from the muscle activity of the patient and element (d) is further defined as means for deriving the complexity of the EEG signal data over a frequency spectrum incorporating the EEG signals and EMG signals for use with a derived measure of EEG signal complexity to determine the hypnotic level of the patient.

39. The apparatus according to claim 28 further including means for providing a signal corresponding to desired cardiovascular characteristics for the patient;

means for obtaining cardiovascular signal data from the patient; means for comparing the cardiovascular signal data of the patient to desired cardiovascular characteristic signal; and means for controlling the anesthetic delivery unit and the administration of the hypnotic drug in accordance with the comparison of the cardiovascular characteristics signal and cardiovascular signal data.

40. The apparatus according to claim 28 further including means in said control unit for establishing a transfer function between the pharmacological effects in the patient and the administration of the drug to the patient for use in controlling said anesthetic delivery unit.

41. The apparatus according to claim 28 further including pharmacokinetic model means in said control unit for use in controlling operation of said anesthetic delivery unit.

42. The apparatus according to claim 28 further including pharmacodynamic model means in said control unit for use in controlling operation of said anesthetic delivery unit.

43. The apparatus according to claim 42 further including pharmacokinetic model means in said control unit for use in controlling the operation of said anesthetic delivery unit.

44. The apparatus according to claim 40 further including pharmacokinetic model means for use with said transfer function means in controlling the operation of said anesthetic delivery unit.

45. The apparatus according to claim 40 further including pharmacodynamic model means in said control unit for use with said transfer function means in controlling the operation of said anesthetic delivery unit.

46. The apparatus according to claim 44 further including

pharmacodynamic model means in said control unit for use with said transfer function means in controlling the operation of said anesthetic delivery unit.

47. The apparatus according to claim 28 further including means for measuring amounts of volatile hypnotic drugs in the breathing gases in the patient and coupled to said control unit for use in controlling the anesthetic delivery unit.

48. The apparatus according to claim 40 further including means for measuring amounts of volatile hypnotic drugs in the breathing gases to the patient, said means being coupled to said transfer function means for use in establishing the transfer function.

49. The apparatus according to claim 40 further including means for obtaining cardiovascular data from the patient, said means being coupled to said transfer function means for use in establishing the transfer function.

50. The apparatus according to claim 28 further including means for providing information relating to one or more of the patient, the hypnotic drug, a medical procedure, and a physician for use in controlling the administration of the hypnotic drug to the patient.

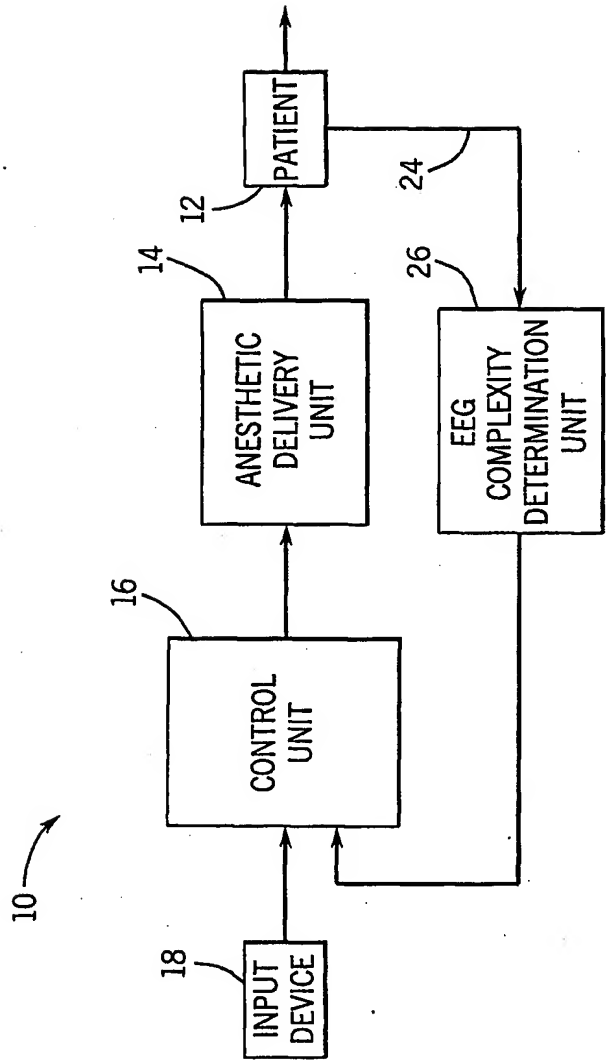
51. The apparatus according to claim 50 further including storage means for storing information relating to one or more of the patient, the hypnotic drug, a medical procedure, and a physician for use in controlling the administration of the hypnotic drug to the patient.

52. The apparatus according to claim wherein the storage means stores information relating to a previous anesthetization of the patient.

53. The apparatus according to claim 50 further including storage means for storing information relating to one or more of the patient, the hypnotic drug, a medical procedure, and a physician for use in controlling the administration of the hypnotic drug to

the patient.

54. The apparatus according to claim 28 including means for generating information in the course of an anesthetization and for employing the generated information in controlling the administration of the hypnotic drug to the patient.


PATIENT
12
24
14
26
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EEG COMPLEXITY DETERMINATION UNIT
16
CONTROL UNIT
10
18
INPUT DEVICE

FIG. 1

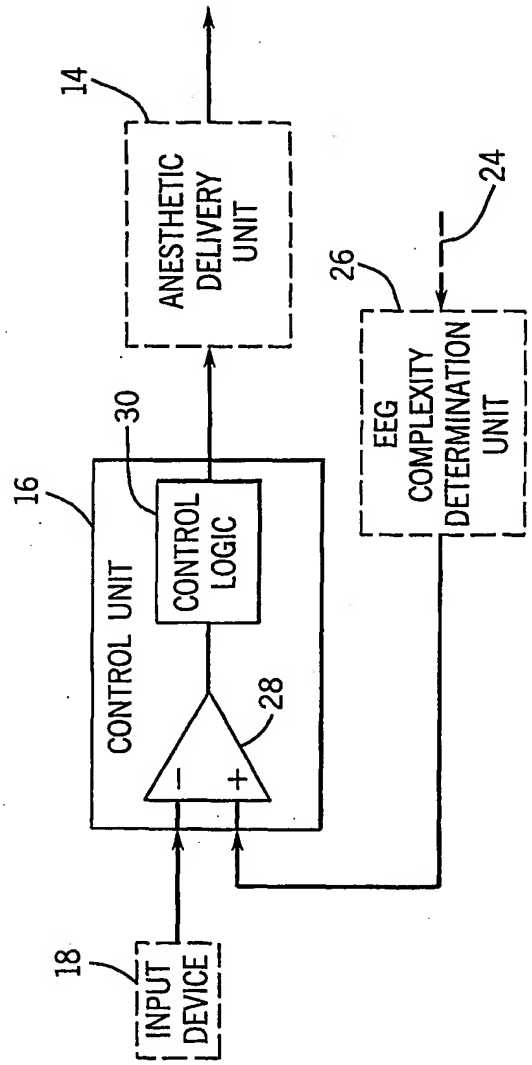
14
ANESTHETIC DELIVERY UNIT
24
26
EEG COMPLEXITY DETERMINATION UNIT
30
16
CONTROL UNIT
CONTROL LOGIC
28
18
INPUT DEVICE

FIG. 1A

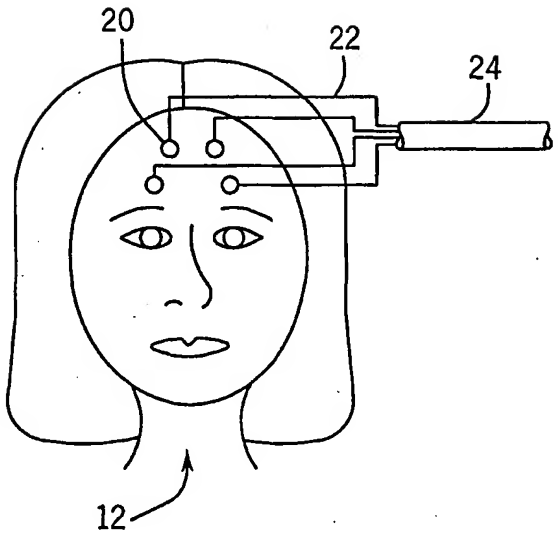

FIG. 2

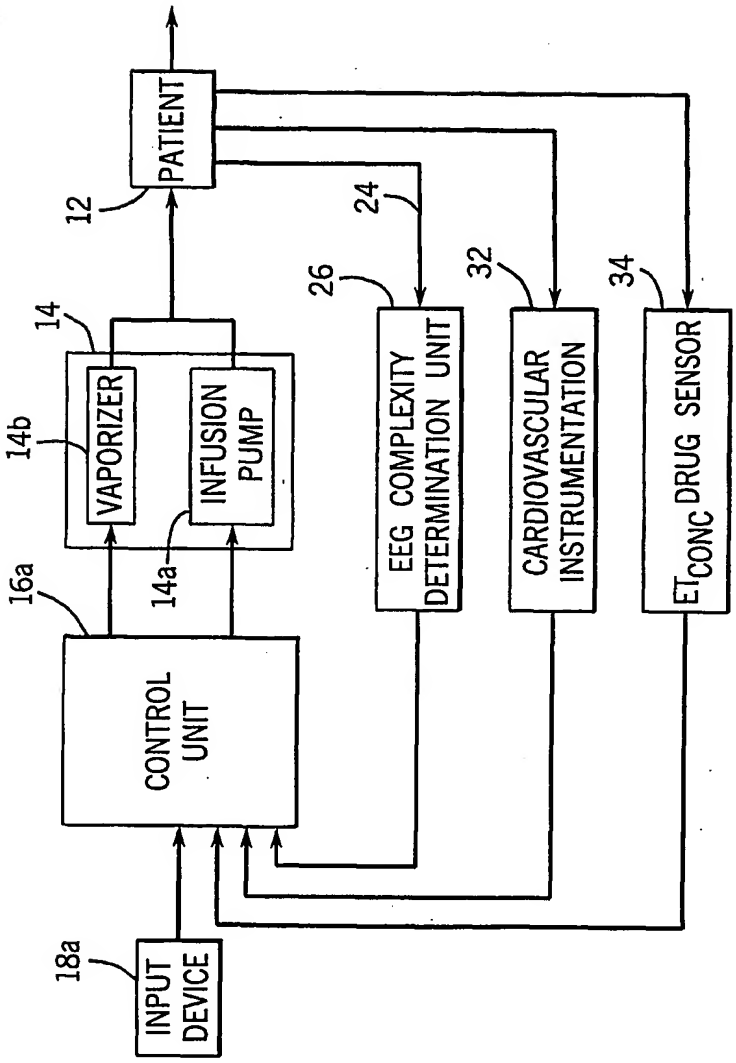
PATIENT
12
24
26
32
34
14
14b
VAPORIZER
INFUSION PUMP
EEG COMPLEXITY DETERMINATION UNIT
CARDIOVASCULAR INSTRUMENTATION
ETCONC DRUG SENSOR
16a
14a
CONTROL UNIT
18a
INPUT DEVICE

FIG. 3

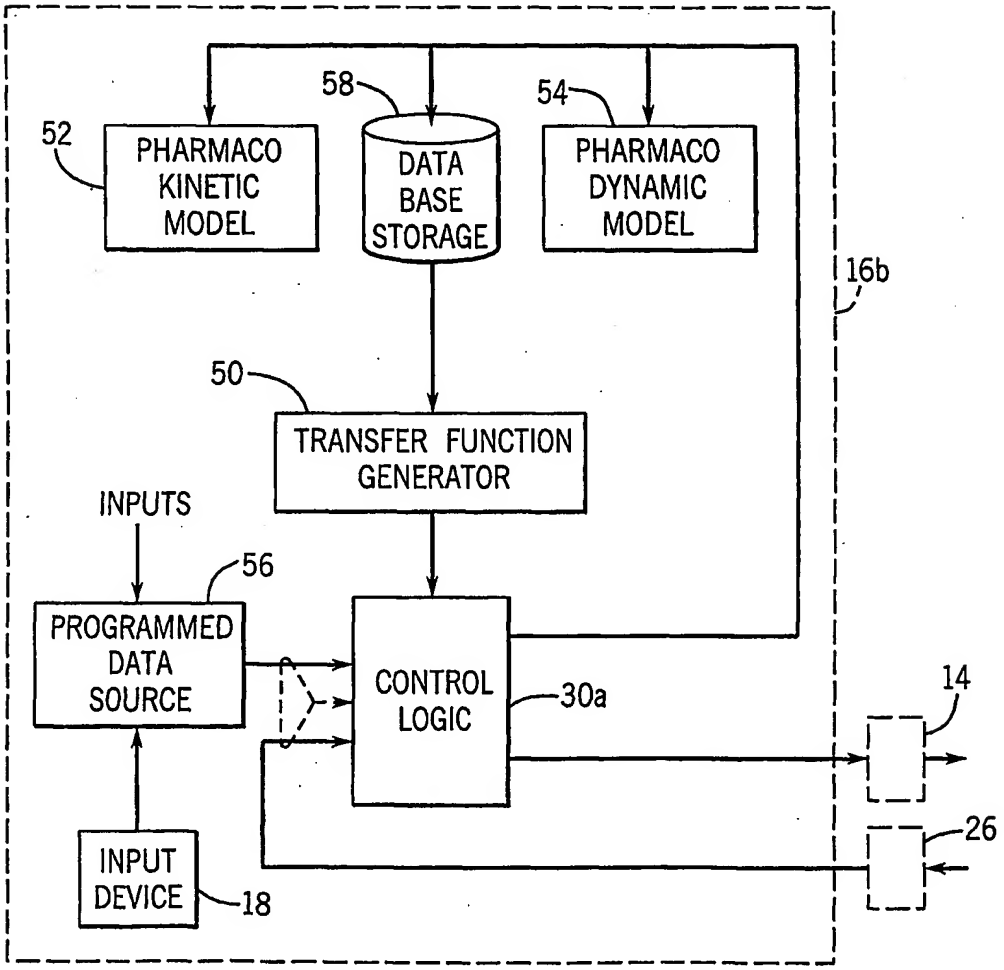
58
54
52
PHARMACO KINETIC MODEL
DATA BASE STORAGE
PHARMACO DYNAMIC MODEL
16b
50
TRANSFER FUNCTION GENERATOR
INPUTS
56
PROGRAMMED DATA SOURCE
CONTROL LOGIC
30a
14
26
INPUT DEVICE
18

FIG. 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 02/01675

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/11

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B A61M G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 016 444 A (JOHN ERWIN ROY) 18 January 2000 (2000-01-18) cited in the application	28
A	column 2, line 52 -column 4, line 6 column 4, line 47 -column 5, line 62 column 6, line 14 -column 14, line 38; table 1	34-36, 38,39, 41,43, 44,47-54
A	GB 2 113 846 A (INSTRUMENTARIUM OY) 10 August 1983 (1983-08-10) abstract page 2, line 19 - line 103 page 3, line 56 -page 4, line 24; table 1	28,34-39

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 September 2002	18/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Weihs, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 02/01675

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 32305 A (INSTRUMENTARIUM CORP) 25 April 2002 (2002-04-25) page 1, line 5 - line 30 page 9, line 5 -page 12, line 4 page 12, line 7 -page 26, line 16; tables 1-10	28-54

2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/01675

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-27
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 02/01675

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 6016444	A	18-01-2000	NONE		
GB 2113846	A	10-08-1983	FI	64281 B	29-07-1983
			DE	3246809 A1	11-08-1983
			FR	2520605 A1	05-08-1983
			IT	1155048 B	21-01-1987
			JP	58133233 A	08-08-1983
WO 0232305	A	25-04-2002	AU	9411601 A	29-04-2002
			WO	0232305 A1	25-04-2002